Familial hypertension and hormonal profile, renal haemodynamics and body fluids of young normotensive subjects


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Summary

1. Almost all the factors that may cause a rise in blood pressure are, in turn, influenced by the increase in blood pressure per se. Thus any primary involvement of one or more of these factors in the pathogenesis of essential hypertension must be evaluated before or during the development of hypertension.

2. Young normotensive subjects both of whose parents are hypertensive have a much higher probability of developing hypertension than those whose parents are both normotensive.

3. The following measurements were made in 56 subjects of the first group (both parents hypertensive) and 35 of the second group (both parents normotensive), matched for age, sex and body surface area: renal plasma flow and glomerular filtration rate, using p-aminohippurate and inulin clearance; 24 h urinary excretion of aldosterone, protein and electrolytes; plasma renin activity; plasma volume. Plasma catecholamines and cardiac index were also measured in 26 subjects of the first group and 25 subjects of the second group using a radioenzymic method and echocardiography.

4. All these factors were similar in the two groups except that renal plasma flow was higher in the first group (767.2 ± 30 versus 650.7 ± 17 ml/min, P < 0.01). Plasma renin activity tended to be lower in subjects with a higher renal plasma flow, but there was no significant negative correlation between the two factors.

5. The possibility that the higher renal plasma flow in subjects with a high probability of developing hypertension is a compensatory mechanism for a primary intrarenal defect is discussed.

Key words: cardiac index, familial hypertension, plasma catecholamines, plasma renin activity, plasma and urinary electrolytes, plasma volume, renal function, urinary aldosterone.

Abbreviation: RPF, renal plasma flow.

Introduction

Hereditary factors seem to play an important role in 'essential hypertension' even though their nature and mechanism of action are unknown (Pickering, 1968). As an approach to this problem the following two groups of observations seem to us to be very pertinent: (1) heredity seems to explain most of the familial similarity in blood pressure in children (Biron, Mongeau & Bertrand, 1976), but the factors responsible for essential hypertension (genetic or environmental) seem to act more effectively in older subjects (around the 4th to 5th decades of life) (Ping-Hwa Hsu, Mathewson & Rabkin, 1976). Assuming that the hereditary factors involved at the two ages are the same, the pattern of blood pressure changes occurring with age in patients with essential hypertension may be due either to a compensatory mechanism which prevents the blood pressure rising before the 4th and 5th decades of life, or to the necessity for the hereditary factors to interact with some environmental or body factors that are peculiar to this age.
(2) Almost all the factors that cause an increase in blood pressure are, in turn, influenced by the increase in blood pressure per se, and the development of hypertension may mask them (Bianchi, Fox, Pagetti, Caravaggi, Baer & Baldoli, 1975; Bianchi, Baer, Fox & Guidi, 1977); thus any primary cause must be detected before or during the development of hypertension. These observations taken together suggest that between the 1st and 4th decades of life the hereditary factors might be detectable in a ‘pure’ state without the secondary changes induced by the rise of blood pressure, or perhaps a compensatory mechanism might be discovered.

To evaluate this hypothesis, the data of a blood pressure survey carried out on the populations of five small towns near Milan were organized according to family trees so that the familial nature of hypertension in young individuals of both sexes could be assessed. Two groups of normotensive subjects, aged 14–30 years and matched for age, sex, body weight, and, when possible, blood pressure were selected. In one group both parents and some relatives had high blood pressure, while in the other group both parents and the great majority of relatives were normotensive. It is probable that about 45% of the subjects in the first group will develop hypertension later in life while only a small minority of the 2nd group (about 3%) should do so (Ayman, 1934).

With these provisos, almost half of the subjects of the first group might be considered to be in the prehypertensive stage whereas those of the second group can be considered as controls. The following factors which are known to be involved in blood pressure regulation were measured: renal plasma flow; glomerular filtration rate; plasma volume; cardiac output; 24 h urinary aldosterone, Na and K; plasma renin activity; plasma Na and K, catecholamines and proteins. This paper described the preliminary results.

Methods

Subjects

A total of 480 family trees were constructed and from this large series 84 family trees were selected belonging to families consisting of two hypertensive parents (blood pressure > 150/95) or two normotensive parents (blood pressure < 140/90) with offspring aged between 14 and 30 years. Blood pressure in the sitting position was measured again in each member of the family by one of two investigators (G.P.L. or M.G.), using a sphygmanometer. The final choice of the families for the groups was also based on the blood pressures of all the known relatives. For the ‘normotensive families’, those with a high incidence of relatives with high blood pressure among relatives were discarded. There were 46 families in the hypertensive group and 37 in the normotensive, and all the offspring aged from 14 to 30 years were candidates for this study. Ten individuals were discarded either because their blood pressure was already high (>160/90) or because they had other diseases, and another 13 declined to co-operate after they learned the purpose and the nature of the study. All other subjects without clinical evidence of renal, cardiovascular or endocrine abnormalities were included in the study, with a total of 65 from hypertensive and 44 from normotensive families. Nine subjects from each group are not considered here for the following reasons: plasma concentration of p-aminohippurate and Inutest not constant after 2 h equilibration, problems of family classification, 24 h urinary protein greater than 150 mg, technical failure. Consent was obtained from the subjects after a detailed description of the procedure had been given.

General procedure

For technical reasons the measurements mentioned in the introduction were carried out on two different occasions and in two different centres on an outpatient basis.

On the first occasion, the following experimental protocol was applied: during the 24 h preceding the measurements the subject was asked to collect urine for the estimation of Na, K, endogenous creatinine clearance, protein and aldosterone, then at 08.00 h, after 30 min in the supine position, the tests were started by taking a blood sample to measure plasma proteins, creatinine, Na, K, renin activity and for blanks. The subject was then asked to empty his bladder and the intravenous infusion of p-aminohippurate and polyfructosan (Inutest, Boehringer, Milan) was started. After an equilibration period of 1 h 45 min Evans Blue was injected and four blood samples were taken at 15 min intervals, for p-aminohippurate, Inutest and Evans Blue estimation. Previous studies did not show any interaction between these measurements. At the end of this period, the subject was again asked to void and the urine obtained was used for p-aminohippurate and Inutest esti-
mations. Blood pressure and heart rate were measured at 1 h intervals. On the second occasion, the cardiac output of 25 subjects from hypertensive families and 24 from normotensive families was measured by the echocardiographic technique in the morning, after the subject had been lying in a supine position in a quiet room for at least 1 h. Blood pressure and heart rate were measured with a sphygmomanometer just before and after the cardiac output measurement. Blood was then taken for estimation of plasma proteins, plasma renin activity and catecholamines. The last two measurements were repeated after 10 min active standing.

Techniques

Plasma and urine Na and K were measured spectrophotometrically. The method of Poulsen & Jørgensen (1973) was used to estimate plasma renin activity. Plasma adrenaline, noradrenaline and dopamine were determined by a highly sensitive radioenzymic method (Da Prada & Zürcher, 1976; Picotti, Buhler & Da Prada, 1977). Urinary aldosterone was measured by radioimmunoassay. Evans Blue was used to estimate plasma volume. Renal plasma flow and glomerular filtration rate were measured by clearance methods, using p-aminohippurate and polyfructosan as markers. A constant infusion technique was applied and RPF and glomerular filtration rate were calculated in the clearance formula from both the rate of intravenous infusion and the rate of urinary excretion. The data given here are those obtained using the rate of intravenous infusion. No correction was made for p-aminohippurate extraction. Cardiac output was determined by echocardiography (Bracchi, Valentini & Piergallini, 1978). All data where body size is relevant were converted into 1.73 m² body surface area. The values are expressed as mean ± SEM.

Results

Group 1 (offspring of hypertensive parents) and group 2 (offspring of normotensive parents) had almost the same age (group 1: 24.6 ± 0.8; group 2: 22.5 ± 0.89 years) the same body surface area (group 1: 1.73 ± 0.19; group 2: 1.73 ± 0.20 m²), and the same haematocrit (group 1: 46.5 ± 0.62; group 2: 45 ± 0.5%). The percentage of females was 30-3 and 34 in group 1 and 2 respectively.

All the other factors measured were also very similar in the two groups, the mean differences being less than 5%, with the exception of RPF which was clearly higher in the offspring of hypertensive parents (767.2 ± 30 versus 650.7 ± 17 ml/min, P < 0.01) who also had a slightly higher diastolic blood pressure (81.9 ± 1.6; 78.2 ± 2.3 mm/Hg, P < 0.05). The range of RPF values in these subjects was much wider than that of controls, and exclusively towards the higher levels. Taking an RPF of 800 ml/min as a dividing line, only 2 of 35 controls had slightly higher values, whereas the values of 22 of 56 offspring of hypertensive parents were above this value. No differences in glomerular filtration rate, cardiac index, plasma volume, or blood pressure were detectable when subjects whose RPF was above 800 ml/min were compared with those whose RPF was below 800 ml/min. The former tended to have lower levels of plasma renin activity than the latter, but borderline statistical significance (P < 0.05) was reached only when the subjects with higher RPF were compared with controls (plasma renin activity: 0.66 ± 0.96; 0.96 ± 0.12 ng/ml/h).

Discussion

The most clear-cut result of our study is the higher RPF found in normotensive subjects with two hypertensive parents, all the other factors measured being equal to those of normotensive subjects with two normotensive parents. With the provisos that we do not know who will have hypertension later in life in the former group, the following four possibilities can be discussed, for the two groups as a whole, while keeping in mind the observations mentioned in the introduction.

1. Since the high RPF was the only abnormality found in subjects with a high probability of developing hypertension, this trait might be the phenotypic expression or part of it, of the gene or genes causing or favouring the development of hypertension when, later in life, interaction with appropriate environmental factors comes into play.

2. Because of some kind of genetic association, the high RPF and hypertension are transmitted together without the existence of a cause–effect relationship between the two traits.

3. The high RPF is caused by unknown environmental factors peculiar to the hypertensive families.

4. The genetic factors work to produce hypertension but the higher RPF prevents their action, or, in other words, the high RPF is a compensatory mechanism.

Possibility 1 is unlikely because, as far as we know, there is no way of raising blood pressure through an increase in RPF. Possibilities 2 and 3...
cannot be proved or disproved at the present state of our knowledge. A difference in sodium consumption is not involved, since 24 h sodium excretion rates were equal in the two groups. Possibility 4, in our opinion, is worth discussing in detail since it may fit with many previous observations. When subjects with high and normal RPF were compared, no difference was found in glomerular filtration rate or arterial pressure. This might indicate that a high RPF in some subjects is required to keep glomerular filtration rate normal. In fact previous studies (Deen, Robertson & Brenner, 1974) clearly showed that the two major determinants of single nephron glomerular filtration rate are single nephron blood flow and effective filtration pressure, the former being more important than the latter. Our studies (Bianchi et al., 1977; Baer & Bianchi, 1978) on the pathogenesis of spontaneous or hereditary hypertension in rats of the Milan hypertensive strain (MHS) indicated that these rats have a lower glomerular filtration coefficient (Kf) before the development of hypertension. Moreover, and this is the most important point, all the observed differences between MHS and normotensive control rats (NR), both before and during the development of hypertension in the MHS, are consistent with the hypothesis that a lower Kf is the primary cause of these differences. If we postulate that in the subjects with higher RPF the genetic factor for the subsequent development of hypertension is a lower Kf, we may explain the increased RPF, the lower plasma renin activity and the development of hypertension later in life in these subjects by the following sequence of events.

In infants below 2 years of age, when a familial aggregation of blood pressure already exists (Yhu-Hsiung-Lee, Rosner, Gould, Lowe & Kass, 1976) and the process of ‘maturation’ of glomerular filtration rate is still in progress (McCrorry, 1972), the lesser delivery of fluid to the macula densa, caused by the lower Kf, resets the glomerulotubular feed-back mechanism to a state of relatively lower intrarenal generation of renin and a relatively higher glomerular blood flow (Wright & Briggs, 1977). Later in life (4th to 5th decades) because of the process of senescence of the renal vascular tree (Hollenberg, Adams, Solomon, Rashid, Abrams & Merrill, 1974) this higher RPF cannot be maintained and the compensation for the lower Kf must be shifted towards an increase in effective filtration pressure, hence hypertension develops. This hypothesis is consistent with many previous findings in essential hypertension, such as the abnormally low plasma renin levels which are unresponsive to various stimuli observed in about 30% of patients; the increased RPF in some young patients with essential hypertension associated with the failure of RPF to decrease with sodium restriction (Hollenberg & Adams, 1976); the greater variability of RPF in the initial stages of hypertension (Hollenberg and Adams, 1976); and the progressive lowering of RPF and plasma renin with increasing age and blood pressure (Birkenhager & Schalekamp, 1976). The later findings are probably linked to an acceleration of the normal age-related reduction in RPF caused by prolonged exposure of the renal arterial tree at first to a higher RPF and later to higher perfusion pressure.

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References


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