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RAPID COMMUNICATION

High Blood Pressure of Hypertriglyceridaemic Rats is Related to Metabolic Disturbances

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Summary

A set of 131 F2 hybrids, obtained from a cross between normotensive Lewis and hypertensive hypertriglyceridaemic (HTG) rats, was studied in order to assess the relationship between blood pressure, plasma triglycerides and plasma uric acid. In progenitors, the plasma levels of triglycerides and uric acid were twice as high in HTG rats than in the Lewis rats. It was observed in the F2 cohort that high mean arterial pressure (MAP) was unrelated to body weight and relative heart or kidney weights. On the other hand, there were significant correlations between MAP and plasma triglycerides ($r=0.420$, $n=131$, $p<0.0001$) and between MAP and plasma uric acid ($r=0.325$, $p<0.001$). Plasma triglycerides of F2 hybrids were below the midparental values, suggesting a stronger influence of normotensive Lewis alleles. In conclusion, hypertension in hypertriglyceridaemic rats strongly cosegregated with plasma triglycerides and plasma uric acid. Our results indicated a linkage between high blood pressure and several metabolic alterations characteristic for the X syndrome.

Key words

Hypertension – Plasma uric acid – Plasma triglycerides – F2 hybrids

Hypertension has many causes, but after a century of clinical and basic research, the discrete explanation of the etiology of hypertension still does not exist. The problem is that the multiple phenotypic differences between hypertensive rat strains and their normotensive controls have usually no relation to hypertension. A better approach than a simple comparison of two inbred strains is to crossbreed normotensive and hypertensive animals to produce a large F2 population (Rapp 1983) or recombinant inbred strains (Kuneš and Zicha 1993) in which individual blood pressure values can be correlated with other measured parameters to look for the relation among the traits of interest. Multiple metabolic abnormalities occur more frequently in hypertensive patients and animals than in their normotensive counterparts (Mondon *et al.* 1988, DeFronzo *et al.* 1991, Reaven 1991). Recently, the direct evidence has been reported that high blood pressure and metabolic disorders are associated in Lyon hypertensive rats (Vincent *et al.* 1993). We have demonstrated that elevated plasma levels of triglycerides are accompanied by high blood pressure in hereditary hypertriglyceridaemic (HTG) rats (Štolba *et al.* 1992) which were selected as a new genetic model of human hypertriglyceridaemia (Vrána *et al.* 1990). The purpose of the present study was to search for the relation between high blood pressure of HTG rats and some metabolic disturbances by means of segregating population derived from HTG and Lewis ancestries.

Normotensive Lewis females and hypertensive HTG males were mated to produce F1 hybrids. Female and male F1 hybrids were paired to provide F2 cohort. Both parental strains and 131 F2 hybrids were used for measurement of blood pressure, plasma triglycerides and plasma uric acid. Rats were housed under controlled conditions (temperature 23±1 °C, 12 h : 12 h light-dark cycle). They were fed a standard rat chow (Velaz, ST-1) containing 0.4% sodium chloride and drank tap water *ad libitum*.

All parameters were studied at the age of 20 weeks. Under ether anaesthesia, a polyethylene

catheter was inserted into the carotid artery, tunnelled subcutaneously and exteriorized at the neck. Blood pressure was recorded in conscious animals after a 24-h recovery period. The arterial catheter was connected to a pressure transducer and 4-channel Hewlett Packard recorder. The system was calibrated before each recording and validated carefully in terms of signal dampening in the catheters. Four animals were recorded simultaneously for one hour. To eliminate the influence of circadian variation in blood pressure, the measurements were done between 0800 and 1200 h each day.

Blood for determination of plasma uric acid and plasma lipids was collected from the tail arteries one day before surgery. All analytic techniques were done by commercial kits (Bio-La-Test, Lachema Ltd., Brno).

Data are expressed as means ± S.E.M. Statistical differences between progenitors were assessed by Student's t-test. Linear regression analysis was used to evaluate the correlation of studied traits. $P < 0.01$ was considered a statistically significant level.

Table 1
Blood pressure, body weight (BW), relative heart (HW/BW) and relative kidney (KW/BW) weights as well as several biochemical parameters in male rats of hypertensive hypertriglyceridaemic (HTG) and normotensive Lewis progenitors

	Lewis (n = 8)	HTG (n = 10)
Systolic blood pressure(mm Hg)	131 ± 3	175 ± 4*
Diastolic blood pressure(mm Hg)	91 ± 3	117 ± 5*
Mean arterial pressure (mm Hg)	108 ± 3	147 ± 4*
Body weight (g)	408 ± 9	329 ± 3*
HW/BW (mg/100 g)	229 ± 3	239 ± 3^{+}
KW/HW (mg/100 g)	650 ± 6	593 ± 11*
Total triglycerides (mmol/l)	1.44 ± 0.25	2.71 ± 0.22*
Plasma uric acid (μmol/l)	67 ± 7	117 ± 13*

*Data are means ± S.E.M., * $p < 0.01$, $^{+}$ $p < 0.05$ significantly different from Lewis strain*

Table 1 summarizes the data from progenitor strains and F2 hybrids. Blood pressure was significantly higher in HTG than in normotensive Lewis rats. There were twofold higher levels of plasma triglycerides and uric acid in HTG rats in comparison with Lewis animals.

Mean arterial pressure (MAP) of F2 hybrids was distributed unimodally and its value (123 ± 1 mm Hg) was below the midparental value. There were no correlations between MAP and relative heart or relative kidney weights ($r = 0.030$ and $r = 0.102$, $n = 131$, N.S.).

In spite of the fact that plasma triglycerides were higher in HTG rats when compared to normotensive Lewis progenitors, plasma triglycerides were significantly lower in F2 population (1.12 ± 0.06 mmol/l) than in Lewis parents. In the F2 cohort, a significant relationship was observed between MAP and total triglycerides (Fig. 1A). Plasma uric acid was also significantly higher in HTG rats than in Lewis ones (Table 1). In F2 hybrids, its mean value (90 ± 5 μmol/l) was not significantly different from the midparental value. The highly significant correlation between MAP and plasma uric acid was demonstrated in F2 cohort (Fig. 1B). Additionally, plasma uric acid correlated significantly with total triglycerides ($r = 0.272$, $n = 131$, $p < 0.01$).

It was demonstrated that plasma triglycerides were higher in both hypertensive patients (McMahon *et al.* 1985) and in rat strains with genetic hypertension (Mondon *et al.* 1988, Mondon *et al.* 1993). To demonstrate the relationship among the traits of interest, crossbreeding experiments are used. The causal relationship between blood pressure and plasma triglycerides was shown for the first time in the F2 cohort derived from Lyon hypertensive and normotensive rats (Vincent *et al.* 1993). Our present work shows that the same relationship was also seen in F2 hybrids derived from HTG and Lewis progenitors. This accordance is very interesting because there was a different origin of HTG rats and Lyon hypertensive rats (Wistar vs Sprague Dawley rats) and the different

reason for the selection of these strains. HTG rats were selected for high plasma triglyceride levels and high blood pressure was found as a consequence of this breeding, whereas in Lyon rats the opposite was true. They were selected for high blood pressure and lipid disturbances were found to be the characteristic traits in this hypertensive strain.

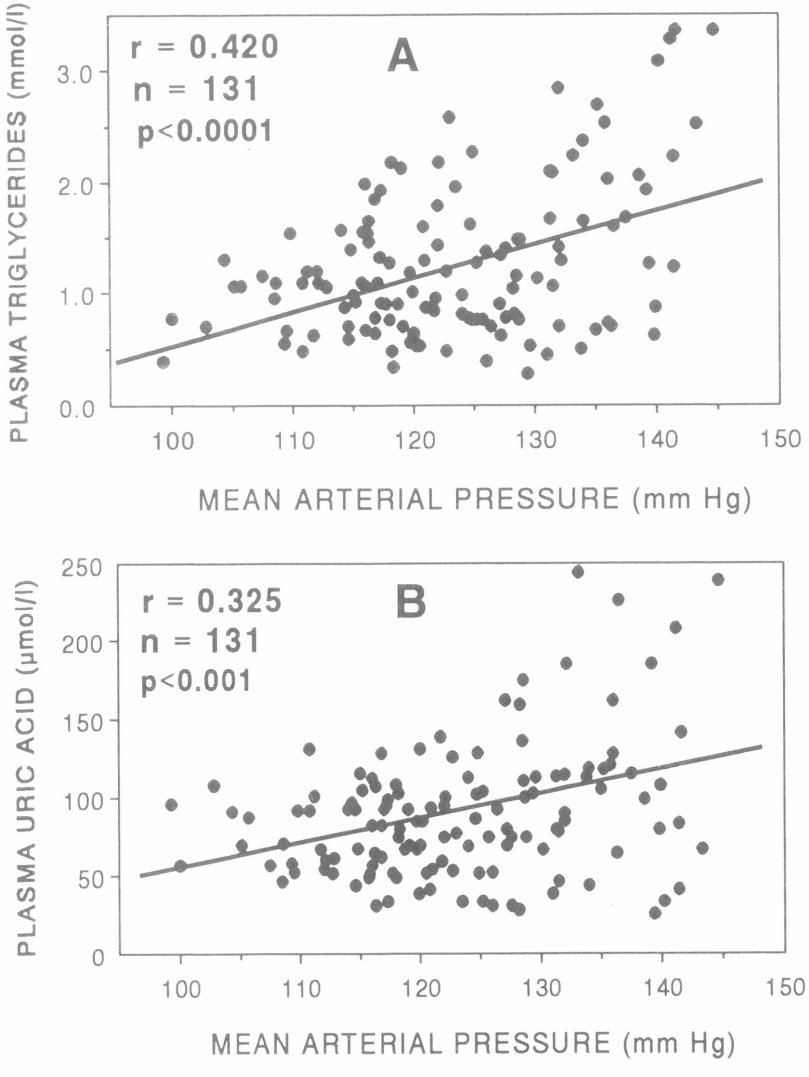

Fig. 1
Relationship between mean arterial pressure and plasma total triglycerides (A) and plasma uric acid (B) in the F2 cohort derived from HTG and Lewis progenitors.

Neither relative heart nor kidney weights were related to MAP in the present F2 cohort. This suggested that MAP itself had no major effect on the weight of these organs. In our previous study on recombinant inbred strains (Kuneš *et al.* 1990) we have also demonstrated the important influence of primary genetic factors regulating intrinsic organ growth rather than secondary blood pressure effects. These findings are in good agreement with the results of several other studies in which the relationship between heart weight and blood pressure was not found (Lindpaintner *et al.* 1990, Harrap *et al.* 1992) or was very weak (Vincent *et al.* 1993).

In conclusion, our study demonstrated that hypertension in hypertriglyceridaemic rats strongly cosegregates with plasma triglycerides and plasma uric acid. Although the evidence for the role of these metabolic disturbances in the pathogenesis of hypertension remains to be elucidated, there is a clear indication of the linkage between high blood pressure and several metabolic alterations characteristic for syndrome X.

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