Lyon genetically hypertensive rats:
an animal model of “low renin hypertension”

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ABSTRACT

This paper reviews the data which demonstrate that Lyon genetically hypertensive (LH) rats exhibit a low renin form of hypertension. Since when compared to normotensive controls, LH rats exhibit a low renin release and are salt-sensitive. Despite this, the blockade of the renin-angiotensin system normalizes the blood pressure level and the regional blood flows in LH rats. Such a discrepancy between the compulsory presence of angiotensin II for the hypertension to develop and the low level of renin release seen in LH rats led to two hypotheses: 1) the existence of an early, short lasting increase of renin release which would be sufficient for the occurrence of a stable hypertension; 2) an hypersensitivity to the effects of angiotensin II. The study of the long-term effects of early short lasting blockades of the renin-angiotensin system allowed to exclude the first hypothesis. Concerning a hypersensitivity to the effects of angiotensin II, it was found to exist in the preglomerular vessels of LH rats. This increased response of renal vessels to angiotensin II may well explain the low renin form of hypertension of our model and therefore represents an important field for further research.

INTRODUCTION

Human essential hypertension is a complex disease which, according to numerous studies, results from the interaction of several genes with environmental factors[1,2]. It can be classified according to the renin secretion in high, normal, and low renin forms[3]. Although this classification is supposed to reflect the sodium status of the patients – from sodium loss to sodium retention – the mechanisms which lead to the low renin form remain to be determined.

Since high blood pressure (BP) is, at least in part, genetically determined, it has been possible to select several strains of genetically hypertensive rats. Among them the Lyon hypertensive (LH) rats have some unique characteristics, one of the most important being the existence of two simultaneously selected normotensive control strains, namely the Lyon normotensive (LN) and low blood pressure (LL) strains[4].

The existence of these two normotensive control strains is due to the fact that, originally[5], we aimed to select three strains with spontaneously differing BP levels: high, normal, and low. It happened that it was not possible to obtain rats with truly low BP and that the corresponding strain (LL) exhibited a BP level similar to that of normotensive controls (LN). However,
this failure turned as an advantage especially for pathophysiologial and genetic studies. In effect, due to the genetic drift during the selection process, each strain differs from another one by nearly 20% of its genome. Therefore it can be assumed that at least 5000 gene differences exist between two strains. As we know that only 5 to 6 genes are involved in the determination of high BP in Lyon rats, the comparison of the hypertensive strain to only one normotensive strain will show 4995 differences which are devoid of physiological significance. Such a difficult situation is markedly improved when the hypertensive strain can be compared to two different normotensive controls, as is the case with LH rats being compared to both LN and LL rats. In those conditions it is possible to differentiate, among the many changes observed between LH and LN rats those which can possibly be related to hypertension — in that case LH differ in the same direction from both LN and LL rats — from those which cannot — in that case LH differ from LN or LL but not from both.

We would like to summarize here the data so far obtained which demonstrate that LH rat is a model of “low renin hypertension,” as well as some experiments performed to address the pathophysiology of their hypertension.

CHARACTERISTICS OF LH RATS

As indicated in Tab 1, plasma as well as kidney renin and prorenin were significantly lower in young adult LH rats compared to controls. The urinary excretion of aldosterone was also significantly decreased, while a markedly lower urinary aldosterone to potassium ratio suggested an enhanced tubular responsiveness to mineralocorticoids. In addition to its low baseline values, renin release in LH rats was found to be poorly responsive to physiological stimuli such as decreases in renal perfusion pressure and β-adrenergic stimulation.

However, despite its low state of release and of response, the renin-angiotensin system was found to be compulsory for the development of hypertension and its associated hemodynamic abnormalities such as increased peripheral resistances with marked vasoconstriction in the splanchic area and especially in the kidneys. In effect, as shown in Fig 1, the systolic BP measured by the tail-cuff method is identical in LH and LN rats treated with an angiotensin converting enzyme inhibitor perindopril (3 mg/kg per 24 h) starting at 3 weeks of age. Interestingly, all the hemodynamic alter-

![Fig 1](image)

Tab 1. Renin, prorenin and aldosterone in 10-week-old LN and LH rats.

<table>
<thead>
<tr>
<th></th>
<th>LN (n=10)</th>
<th>LH (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>renin (ng AI/h/ml)</td>
<td>32±4</td>
<td>15±2***</td>
</tr>
<tr>
<td>prorenin (ng AI/h/ml)</td>
<td>54±5</td>
<td>33±3**</td>
</tr>
<tr>
<td><strong>Kidney:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>renin (µg AI/h/mg protein)</td>
<td>3.2±0.4</td>
<td>1.9±0.1**</td>
</tr>
<tr>
<td>prorenin (µg AI/h/mg protein)</td>
<td>3.7±0.2</td>
<td>2.1±0.2***</td>
</tr>
<tr>
<td><strong>Urinary:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aldosterone (ng/24h)</td>
<td>3.4±0.3</td>
<td>2.0±0.1**</td>
</tr>
<tr>
<td>aldosterone/K+</td>
<td>1.47±0.09</td>
<td>0.74±0.04***</td>
</tr>
</tbody>
</table>

**P<0.01; ***P<0.001 versus LN rats
ations which characterize LH rats disappeared after perindopril treatment.

Since the kidney plays a major role in the development of hypertension through the characteristics of the pressure-natriuresis curve which determines the long term BP level, we studied the renal functions of LH rats at several levels of perfusion pressure by using the technique described. In those experimental conditions, LH rats differ from controls by a significantly lower renal blood flow and glomerular filtration rate associated with a blunted diuretic and natriuretic response to renal perfusion pressure increase (Fig 2). Once more, the inhibition of the formation of angiotensin II with perindopril given from weaning normalizes all the renal parameters studied.

Finally, as frequently observed in patients with a low renin form of essential hypertension, LH rats have been found to be salt-sensitive, as after 3 weeks of 2% NaCl in the drinking water, the indirect systolic BP of LH rats is elevated by 40 mmHg compared to 10 mmHg in LN and LL control rats.

In order to explain the paradoxical association of a low activity of the renin-angiotensin system with the compulsory presence of angiotensin II for the hypertension to develop in LH rats, we formulated two hypotheses. First, the existence of a transient early increase in the activity of the renin-angiotensin system which will be sufficient to allow the long term development of hypertension despite the disappearance of this overactivity. Second, an increased sensitivity of LH rats to the effects of angiotensin II.

**LACK OF EXISTENCE OF AN EARLY SHORT LASTING INCREASE IN RENIN-ANGIOTENSIN SYSTEM ACTIVITY IN LH RATS**

The first hypothesis was primarily suggested by the fact that in a previous experiment, plasma renin activity was higher in young LH than LN rats. In addition, this hypothesis was theoretically made possible by the fact that, besides vasoconstrictory and aldosterone stimulating properties, angiotensin II exerts a durable influence on the vessels and the kidneys through the stimulation of several growth factors. Finally, it was strengthened by the repeated observations that an early short lasting blockade of the renin-angiotensin system in Japanese spontaneously hypertensive rats (SHR), induced decreases in BP which remained significant several weeks after cessation of the blockade.

**Fig 2. Effects of renal perfusion pressure (RPP) on renal blood flow (RBF), glomerular filtration rate (GFR), urinary volume (UV), and urinary sodium excretion (UNaV) in 8-wk-old LH and LN rats.** * P<0.05, *** P<0.001 versus LN rats at a similar level of RPP.
In order to test this hypothesis in LH rats, we designed two treatment protocols. In a first one, LH rats were treated from conception up to weaning (3 weeks of age) with captopril (100 mg/kg per 24 h) given to the parents[18]. Captopril was chosen since it was demonstrated to be excreted in the milk and thus allowed the blockade of the production of angiotensin II in the pups. The second one used perindopril (0.4 or 3 mg/kg per 24 h) and losartan (10 mg/kg per 24 h), an angiotensin type 1 receptor antagonist. Drugs were administered from 3 to 12 weeks of age, i.e., during the period of fast rise of BP in LH rats. In both protocols, systolic BP was measured by the tail-cuff method. SBP of LH rats having received captopril from conception to weaning was significantly higher than that of never treated age matched controls (Fig 3). In the same way, in LH rats treated from weaning to 12 weeks of age, SBP returned to the level of never treated animals in approximately one week after treatment withdrawal.

Those two experiments allowed to exclude that an early burst of activity of the renin-angiotensin system could explain the long term development of hypertension in LH rats. They also demonstrated that the persistent effect of renin-angiotensin system blockade observed in SHR was not a generalized property but might rather be specific to the Japanese strain.

SENSITIVITY TO THE EFFECTS OF ANGIOTENSIN II

In search for an elevated response, the overall sensitivity of LH rats to the vasoconstrictor effects of angiotensin II was studied in carefully controlled conditions. We used conscious rats, the BP of which was measured beat to beat through a chronically inserted aortic catheter. They received 10 iv bolus of angiotensin II so as to determine the dose-response curve[8]. LH rats differed from LN controls by an increase in the maximum effects of angiotensin II which is likely to reflect the hypertension induced hypertrophy of the cardiovascular system (Fig 4). However, the sensitivity to angiotensin II, as measured by the ED$_{50}$, did not significantly differ between the strains.

Facing this lack of generalized oversensitivity to the vasoconstrictor effects of acutely given angiotensin II, we examined more specifically the sensitivity of renal vessels. This was performed using anaesthetized rats maintained since weaning at the same level of BP by treatment with perindopril[12]. Two doses of angio-
tensin II (10 and 50 ng kg\(^{-1}\) min\(^{-1}\)) were infused which allowed to demonstrate (Fig 5) that at a given renal perfusion pressure level, LH kidneys responded by a significantly larger decrease in renal blood flow, glomerular filtration rate and natriuresis than controls. This clearly demonstrates that the vessels and more specifically, the preglomerular vessels of LH kidneys are hypersensitive to the effects of angiotensin II. Such an increased sensitivity is unlikely to be secondary to hypertension-induced renal damages since LH rats were maintained normotensive with perindopril. Therefore, it is possible to suggest that the enhanced renal sensitivity to angiotensin II plays a primary role in the pathogenesis of hypertension in our model. The next challenge is to determine the mechanisms of this local hypersensitivity in order to disclose a potential new target for the treatment of "low renin hypertension."

REFERENCES

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![Fig 5. At 90 mmHg of renal perfusion pressure (RPP), acute effects of angiotensin II (AII) on renal blood flow (RBF), glomerular filtration rate (GFR), and urinary sodium excretion (UNaV) in 15-wk-old LH and LN rats treated with perindopril from 3 to 15 weeks of age. AII was infused at a rate of 10 (AII-10) or 50 (AII-50) ng/kg/min. * P<0.05, ** P<0.01 versus LN rats[21].](image)


