Blood Pressure, Heart Rate and Motor Activity in 6 Inbred Rat Strains and Wild Rats (Rattus norvegicus): A Comparative Study

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Abstract: Inbreeding for many generations under optimal environmental conditions may have favoured the survival of alleles for blood pressure increase in phenotypically normotensive rat strains. To prove this hypothesis we measured telemetrically systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR) and motor activity (MA) in 6 inbred rat strains (BB, BN, LEW, DA, F344, WKY) and wild rats most probably possessing all of the alleles for normotension. For the first time it is shown that systolic blood pressure can significantly differ between normotensive inbred rat strains and that most probably some inbred rat strains will be characterised by a systolic blood pressure found in their progenitors, the wild rats. In addition, the typical night activity of rodents was not seen in 2 inbred rat strains. All findings together may be interpreted in the sense that most, if not all inbred rat strains have more or less disturbances in blood pressure, HR and/or MA and that there is most probably no "healthy" inbred rat strain available so that wild rats may be an alternative for crossing studies dissecting hypertension in particular and diseases in general.

Key words: blood pressure, heart rate, motor activity, inbred rats, wild rats

Introduction

Human primary hypertension is one of the most common chronic diseases recognised as a complex, polygenic disorder. The nature of complex diseases makes it very difficult to identify contributing genes. Therefore, inbred animal models have been used to identify discrete genetic factors contributing to primary hypertension. For this purpose hypertensive and normotensive rat strains are normally crossed. With the aid of such segregating crossing populations it is possible to map chromosomal regions containing a quantitative trait locus for blood pressure regulation in genetically hypertensive rat strains. Nevertheless, in comparing the results of such segregating crossing populations with the same hypertensive rat model but different normotensive rat strains, it becomes clearly that mapping results do not need to be consistent for different crosses [3, 4, 6, 12–15]. This fact may be attributed to the normotensive rat strains. Considering that inbreeding for many generations un-
der optimal environmental conditions may have favoured the survival of alleles for blood pressure increase in normotensive rat strains without striking phenotypic consequences, the normotensive rat strains used in crossing studies should differ not only in the genotype but also in the phenotype “normotension”. That prompted us to compare the blood pressure, heart rate and motor activity of 6 inbred rat strains known to be normotensive and wild rats (Rattus norvegicus) which, in contrast to the inbred rat strains, should not possess “silent” alleles for hypertension.

**Material and Methods**

**Animals:** Males of the inbred rat strains BB/OK (n=6), DA/K (n=5) and LEW/K rats (n=6) bred in our own animal facility [8, 9] and BN/Crl (n=5), F344/Crl (n=5) and WKY/Crl (n=6) rats commercially obtained from Charles River Wiga GmbH (Sulzfeld, Germany) as well as male wild rats (n=6) captured in North Germany as described [10] descending from the 3rd generation bred under laboratory conditions in our own animal facility were studied. Because BB/OK rats can develop an insulin-dependent diabetes mellitus, non-diabetic BB/OK rats were used [8]. All rats were kept under strict hygienic conditions in the same animal unit and were free of major pathogens as described elsewhere [8]. The animals had free access to food (Ssniff R, Soest, Germany) and acidulated water and were kept on a 12 hr light (5 a.m. to 5 p.m.): 12 hr dark rhythm. The animal rooms had air conditioning with an temperature of 22 ± 2°C and a humidity of 60 ± 5%.

**Transmitter implantation:** Animals at 10 weeks of age were surgically prepared under Rompun® (Bayer, Germany) and Ketamin® (Sanofi, Germany) combination anaesthesia and sterile conditions. The transmitters (Model TA11PA-C40, Data Sciences International, St Paul, MN, USA) were implanted as described in detail [1]. After the operation the rats were housed in individual cages (Size 3, Ehret GmbH, Emmendingen, Germany).

**Telemetry and data acquisition:** The telemetric measurement was started 10 days after surgery and was performed twice for 4 days with an interval of 7 days. The Dataquest IV telemetry system (Data Sciences International, St Paul, MN, USA) was used for telemetric measurement of systolic (SBP, mmHg) and diastolic blood pressure (DBP, mmHg), heart rate (HR, beats/min) and motor activity (MA, movements/min). The measurements were carried out every 5 min per day and animal as mentioned above.

**Data analysis:** For data processing DQSORT program (Data Sciences International, St Paul, MN, USA) and the statistical analysis system SPSS were used. A single daytime mean (inactive phase) and a single nighttime mean (active phase) were calculated for each rat and checked for significance. For the analysis of the day profiles mean values were calculated for each strain in dependence on 5-min-interval measurements over 24 hr (288 values p. strain). The values for blood pressure, heart rate and motor activity are given as the mean ± SD. Significant differences between mean values were checked by the t-Test (confidence interval=95%).

**Results**

As demonstrated in Table 1, summarising the daytime (light) and nighttime (dark) values for each strain and trait studied, the systolic (SBP) and diastolic blood pressure (DBP), pulse pressure (PP) and heart rate (HR) of BB/OK rats are comparable with those of wild rats. The daytime SBP values differ only by 1 mmHg (112 vs. 113) and the nighttime values are identical (116 vs. 116 mmHg). In contrast to BB/OK rats which differ from wild rats only in the MA, the other rat strains differ significantly from wild rats in the HR (BN, LEW, WKY) (Fig. 2) and in the MA (BN, LEW, DA, F344) (Fig. 3) and show differences also between BB/OK and wild rats in SBP (BN, LEW, DA, F344, WKY) (Fig. 1) and DBP (BN, LEW, DA, F344). Although no significant differences in SBP and DBP were found between wild and inbred rat strains, significant differences were observed between the inbred rat strains (cf. Table 1). Comparing the values for the inbred rat strains, two groups in SBP can be differentiated. Lowest values were found in BN and LEW rats and highest in DA, F344 and WKY rats. The SBP differences are statistically significant for both groups, differing by about 20 mmHg. In comparison with wild rats, this difference of 20 mmHg may suggest that BN and LEW rats are more prone to hypotension and DA, F344 and WKY rats more prone to hypertension. In DBP similar groups can be observed, but not so pronounced as found for SBP. Because of this fact, the PP is generally similar.
Table 1. Systolic (SBP) and diastolic blood pressure (DBP), pulse pressure (PP), heart rate (HR) and motor activity (MA) in wild and 6 inbred rat strains

<table>
<thead>
<tr>
<th></th>
<th>Wild (n=6)</th>
<th>BB (n=6)</th>
<th>BN (n=6)</th>
<th>LEW (n=6)</th>
<th>DA (n=5)</th>
<th>F344 (n=5)</th>
<th>WKY (n=6)</th>
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<tr>
<td>SBP (mmHg)</td>
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<tr>
<td>Daytime</td>
<td>112 ± 9</td>
<td>113 ± 6</td>
<td>100 ± 11</td>
<td>105 ± 7</td>
<td>120 ± 5</td>
<td>119 ± 5</td>
<td>121 ± 3</td>
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<td></td>
<td>116 ± 10</td>
<td>116 ± 6</td>
<td>102 ± 10</td>
<td>106 ± 7</td>
<td>125 ± 10</td>
<td>123 ± 5</td>
<td>124 ± 3</td>
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<td>Nighttime</td>
<td></td>
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<tr>
<td>DBP (mmHg)</td>
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<tr>
<td>Daytime</td>
<td>82 ± 10</td>
<td>85 ± 8</td>
<td>73 ± 15</td>
<td>75 ± 7</td>
<td>91 ± 11</td>
<td>88 ± 4</td>
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<td>28 ± 7</td>
<td>27 ± 12</td>
<td>30 ± 10</td>
<td>30 ± 16</td>
<td>31 ± 7</td>
<td>36 ± 4</td>
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<td>28 ± 7</td>
<td>28 ± 13</td>
<td>30 ± 6</td>
<td>30 ± 15</td>
<td>30 ± 7</td>
<td>36 ± 4</td>
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<td>HR (Beats/min)</td>
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<tr>
<td>Daytime</td>
<td>329 ± 14</td>
<td>333 ± 22</td>
<td>366 ± 11</td>
<td>348 ± 8</td>
<td>369 ± 13</td>
<td>372 ± 17</td>
<td>340 ± 7</td>
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<td>Nighttime</td>
<td>358 ± 23</td>
<td>370 ± 11</td>
<td>372 ± 14</td>
<td>353 ± 9</td>
<td>401 ± 22</td>
<td>405 ± 15</td>
<td>372 ± 12</td>
</tr>
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<td>MA (Movements/5 min)</td>
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<td>19 ± 7a</td>
<td>11 ± 5ab</td>
<td>15 ± 2a</td>
<td>21 ± 7a</td>
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<tr>
<td>Nighttime</td>
<td>37 ± 10</td>
<td>27 ± 6</td>
<td>24 ± 5</td>
<td>22 ± 8</td>
<td>25 ± 7</td>
<td>34 ± 6</td>
<td>43 ± 9</td>
</tr>
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</table>

* significant difference between the daytime and nighttime values (~5%, *~1%). ** significant difference between wild and inbred rat strains (~5%, *~1%). *** significant difference between BB and the other inbred rat strains (~5%, *~1%). **** significant difference between BN and DA, F344, WKY (~5%, *~1%). ***** significant difference between LEW and DA, F344, WKY (~5%, *~1%). ****** significant difference between DA and WKY (~5%, *~1%). ******* significant difference between F344 and WKY (~5%, *~1%).

Systolic blood pressure

Fig. 1. Day profiles of systolic blood pressure of 6 inbred rat strains and wild rats.
Fig. 2. Day profiles of heart rate of 6 inbred rat strains and wild rats.

Fig. 3. Day profiles of motor activity of 6 inbred rat strains and wild rats.
in all the rat strains, except for the WKY rats. The PP of WKY rats is the highest found among the rat strains tested, but only significantly different from BB rats. In this rat strain also significant differences were found between day- and nighttime values in SBP and DBP.

In contrast to blood pressure values, greater differences between the rat strains were not only observed in HR and MA per se but also between the day- and nighttime values. Significant differences between the day- and nighttime HR values were found in wild, BB, DA, F344 and WKY rats. No differences were observed in BN and LEW rats. In comparison with wild rats, significantly higher HRs were found in BN and LEW for daytime, but not for nighttime values. The day- and nighttime values differed only between wild and DA and F344 rats. Although rats are night active animals, the HR of BN and LEW rats does not indicate an influence of the light and dark phase. The day- and night time values were comparable. This phenomenon is also seen in the MA of LEW rats. There were no changes between day- and nighttime values. Comparing the day- and nighttime values for MA in wild and inbred rats, only WKY rats were characterised by a comparable MA also found in wild rats in both, day- and nighttime values.

On analysing correlations between blood pressure, HR and MA there were obviously differences between wild and inbred and among inbred rat strains. In wild rats SBP and DBP correlated in day- and nighttime values (r=78, p<0.05) which was not found in any inbred rat strain. Furthermore, the daytime PP and MA values were negatively correlated in wild rats (r=−.94, p<0.01), but were positively correlated in BN rats in day- and nighttime values (r=.88, p<0.05). In the other rat strains there were no correlations between PP and MA, but correlations between nighttime values of SBP and HR as well as MA (r=.86, r=.83 p<0.05) and also of HR and MA in WKY rats (r=.84 p<0.05). The latter was also found in DA rats (r=.84, p<0.05). Significant correlations were also found between SBP and HR (daytime r=.89 p<0.05) and between PP and MA in BN rats (nighttime, r=.88 p<0.05).

**Discussion**

In contrast to the genetically hypertensive rat strains which have been extensively characterised for pheno-
types [5, 7, 11], there are only a few phenotypic data comparing the blood pressure of normotensive rat strains measured at the same time and under the same experimental conditions [2]. We have therefore studied 6 normotensive inbred rat strains and wild rats to prove intrastrain differences in SBP, DBP, PP, HR and MA on the one hand and to prove their phenotypic change after inbreeding by the comparative study of wild rats representing the wild-types of traits studied. For the first time it is shown that systolic blood pressure measured in unrestrained and free-moving rats can significantly differ between normotensive inbred rat strains and that most probably few inbred rat strains will be characterised by a systolic blood pressure found in their progenitors, the wild rats, Rattus norvegicus. Only in 1 (BB) out of 6 inbred strains a systolic and diastolic blood pressure as well as heart rate were measured which were comparable to some extent with those of wild rats. The remaining 5 strains can be divided in 2 groups. BN and LEW rats are more “hypotensive” and DA, F344 and WKY are more “hypertensive” rat strains. In addition, BN and LEW rats seems to have lost the typical night activity of rodents, for their blood pressure values, HR and MA did show the lowest changes between day- and nighttime values, especially pronounced in the HR. Whereas wild, BB, DA, F344 and WKY rats reacted with a HR increase of about 30 beats/min after switching from a light (rest) to a dark (active) phase, BN and LEW rats reacted only with an increase of about 5 beats/min. Interestingly also the findings in the MA, where LEW rats did not show, and BN showed a small increase in their activity in the dark phase. Compared with the wild rats, LEW rats have totally, and BN have partially lost their night activity during inbreeding. Also the correlations between SBP, DBP, HR and MA were informative. Especially the correlations between SBP and DBP only found in wild rats may be interpreted in the sense that in all inbred rat strains studied the natural relation between SBP and DBP was lost during the inbreeding process over many generation and therefore, most, if not all inbred rat strains have more or less disturbances in blood pressure, HR and/or MA, or in other words, there is most probably no actually “healthy” inbred rat strain available. Therefore, wild rats, which should represent a “healthy” genotype and phenotype may be an alternative for crossing studies to map genes for blood pressure regulation in particular and disease genes in general.
Acknowledgments

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