Selective Breeding to Develop Lines of Baboons With High and Low Blood Pressure


Lines of baboons with high and low blood pressure were developed by selective breeding. Blood pressure was measured in 456 adult feral baboons under ketamine immobilization by direct arterial cannulation. Males with blood pressures two standard deviations and females with blood pressures one standard deviation above and below the cumulative mean were selected as progenitors. High males were mated with high females and low males were mated with low females. We measured blood pressure and plasma renin activity on 100 progeny, 54 males and 46 females, greater than 44 months of age with an abbreviated tether protocol and software program for data collection. Mean systolic and diastolic nighttime pressures for the high line were 126/72 and for the low line were 114/65 mm Hg. Line differences for systolic (12 mm Hg) and for diastolic (7 mm Hg) pressures were significant (p<0.001). The line difference for plasma renin activity (1.1 [ng/mL]/hr) was not significant. Progeny pressures ranged from 84/49 to 191/126 mm Hg. There was no sex effect on blood pressure or plasma renin activity line differences. Heritability of systolic pressure was 0.46±0.19 and of diastolic pressure was 0.22±0.19. These results indicate that, by selective breeding and rigorous measurement of blood pressure, lines of baboons with significant differences in blood pressure can be developed. 

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KEY WORDS • papio • blood pressure • plasma renin activity • breeding

Genetic factors in blood pressure (BP) are well established in both humans and several species of animals.1-6 Our objective was to develop lines of baboons with high and low BP by selectively breeding animals with naturally occurring variations in BP levels. The comparison of families of baboons with contrasting phenotypes would be more valuable for probing physiological, biochemical, metabolic, and genetic factors associated with blood pressure control than the comparison of animals with elevated pressures to a control population. The focus of this report is 100 baboons who were the progeny of the select breeding colonies.

Methods

Breeding Colony Development

Progenitors were selected from 229 male and 227 female adult feral baboons, Papio cynocephalus anubis and Pc cynocephalus, that were characterized between 1975 and 1980. Direct BP was measured by percutaneous arterial cannulation while the animal was under ketamine immobilization. We selected 12 males whose systolic and diastolic BPs were two standard deviations above or below the cumulative mean and 32 females whose BPs were one standard deviation above or below the cumulative mean. Based on these criteria, we identified eight high and four low males and 21 high and 11 low females. High males were mated with high females and low males were mated with low females. As the breeding program progressed, animals with more extreme pressures were identified from feral and Foundation-born animals, and they were added to the breeding colonies. Progeny described in this report are produced by eight sires (five high and three low) and 44 dams (24 high and 20 low).

Animal Maintenance

Breeding colonies were maintained in harems consisting of a male and 12-20 females in outside gang cages with 6,000 cu ft of living space. Water was available through automatic watering devices, and commercially prepared monkey chow (Ralston Purina Company, St. Louis, Mo.) that contained 0.2% sodium and 0.9% potassium was fed daily. Infants were maintained with their mothers until about 6 months of age when they were housed with age peers for the next 30 months. Sexes were separated at 3-3.5 years of age when females undergo menarche. At about 44 months of age, animals were moved to individual cages in the tether laboratory to measure their BP. Temperature was kept at 68-72°F, and a 12-hour light/dark cycle, 6 AM to 6 PM, was maintained in animal bays.

Progeny Characterization

We used an abbreviated tether protocol and software program for data collection to sample and collect data on 100 pedigreed baboons, 54 males and 46 females. The tether, a modification of the device described by Byrd,7 allows the sampling and continuous monitoring of conscious unrestrained animals and avoids the confounding effects of ketamine on BP and neurohumoral hormones. The tether protocol consisted of fitting the
backpack, allowing 2 weeks for adjustments and acclimatization, surgically implanting catheters in the internal iliac artery and vein and 2 weeks for recovery. BP measurements were collected from 6 PM to 6 AM on Thursday through Monday for 2 weeks. In a subset of 13 progeny, seven high line and six low line, daytime BP measurements from 9 AM to 3 PM were also collected. After each 4-day recording session, a blood sample was drawn to determine plasma renin activity (PRA). All experimental procedures were approved by the Southwestern Foundation Animal Care and Use Committee. All statistical analyses were performed using a nonparametric two-sample test.

Data Collection

Systolic, diastolic, and mean BP and heart rate measurements were collected every second using a Gould pressure processor as a signal conditioner and a 286 PC microcomputer with a 16-channel analog-digital conversion board for computerized data collection. Eight 12-hour recording sessions produced 1,382,400 measurements from high line and low line sibships, and values for the low line are the average of five sire sibships. Nonparametric statistical analysis of the three measures of BP, heart rate, and PRA revealed no significant differences among sires within lines. However, there were significant differences between the high and low lines for all three measures of BP. High line BP averaged 10% higher than low line. Individual pressures ranged from 84/49 to 191/126 mm Hg. Heritability of systolic pressure was 0.46±0.19; of diastolic pressure, 0.32±0.18; and of mean pressure, 0.44±0.19. The line differences for PRA (1.1 [ng/mL]/hr) and for mean heart rate were not significant.

We simultaneously estimated the effects of gender on the three measures of BP, as well as the proportion of variance due to genetic factors (i.e., heritability) using maximum likelihood methods. BP measurements for individual (yi) were modeled as follows:

\[ y_i = \mu + \beta_{\text{gender}} + g + e \]

where \( \mu \) is the overall mean and \( \beta_{\text{gender}} \) is the regression coefficient for differences between genders. The parameters \( g \) and \( e \) are the deviations from \( \mu \) for individual (i) due to the residual polygenic and environmental factors, respectively. The effects \( g \) and \( e \) are assumed to be independent and normally distributed, with mean zero and variance \( \sigma_g^2 \) and \( \sigma_e^2 \). The heritability was estimated from the covariance matrix.

Results

Table 1 compares the systolic, diastolic, and mean BP and heart rate measurements of 53 high and 47 low line progeny. Values for the high line are the average of five sire sibships, and values for the low line are the average of three sire sibships. Nonparametric statistical analysis of the three measures of BP, heart rate, and PRA revealed no significant differences among sires within lines. However, there were significant differences between the high and low lines for all three measures of BP. High line BP averaged 10% higher than low line. Individual pressures ranged from 84/49 to 191/126 mm Hg. Heritability of systolic pressure was 0.46±0.19; of diastolic pressure, 0.32±0.18; and of mean pressure, 0.44±0.19. The line differences for PRA (1.1 [ng/mL]/hr) and for mean heart rate were not significant.

There were no significant sex differences for three measures of BP and PRA. Heart rate in females was significantly higher (\( p<0.05 \)) than that in males in both high line and low line.

Figure 1 depicts the distribution of individual mean BP measurements of high and low line male and female baboons. The means of the high line (95±13) and low line (86±08) were significantly different (\( p<0.001 \)). There was no sex effect on high or low line group means.

### Table 1. Blood Pressure, Heart Rate, and Plasma Renin Activity of Male and Female Baboons Selectively Bred for High and Low Blood Pressure

<table>
<thead>
<tr>
<th>Line</th>
<th>n</th>
<th>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
<th>Mean (mm Hg)</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30</td>
<td>128±17</td>
<td>71±13</td>
<td>95±14</td>
<td>74±15</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>124±09</td>
<td>72±08</td>
<td>95±08</td>
<td>82±12</td>
</tr>
<tr>
<td>Line mean</td>
<td></td>
<td>126±14</td>
<td>72±11</td>
<td>95±13</td>
<td>77±14</td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24</td>
<td>112±10</td>
<td>63±06</td>
<td>84±07</td>
<td>71±10</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>117±08</td>
<td>66±06</td>
<td>88±06</td>
<td>75±10</td>
</tr>
<tr>
<td>Line mean</td>
<td></td>
<td>114±10</td>
<td>65±06</td>
<td>86±08</td>
<td>73±11</td>
</tr>
</tbody>
</table>

*Statistical significance of the differences between the high and low line groups as indicated by a nonparametric two-sample test.

HR, heart rate; bpm, beats per minute; n, number of animals.

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There were no significant sex differences for three measures of BP and PRA. Heart rate in females was significantly higher (\( p<0.05 \)) than that in males in both high line and low line.

Figure 1 depicts the distribution of individual mean BP measurements of high and low line male and female baboons. The means of the high line (95±13) and low line (86±08) were significantly different (\( p<0.001 \)). There was no sex effect on high or low line group means.
FIGURE 1. Plot shows mean blood pressures of 100 male and female baboons selectively bred for high and low blood pressure. Solid lines between groups represent high and low line means and standard deviations. Each group's mean value is represented by a solid line within the group.

There was considerable overlap of pressures for progeny from the high and low line.

Table 2 lists the sires and number of progeny in each sire's BP is listed.

Systolic, diastolic, and mean BP values of sire sibships revealed no significant difference of mean values among high or low sire sibship lines when analyzed by nonparametric tests. Mean BP averages for sire sibships of high line were equal to or greater than 92 mm Hg; mean BP averages for the low line were equal to or less than 89 mm Hg.

Table 3 compares systolic, diastolic, and mean BP and heart rate measured with the tether system during night and day in a subset of 13 animals.

For both lines of animals, there was a significant decrease in pressures and heart rate from daytime to nighttime. Pressure and heart rate decreases were greater for the low line than for the high line. Low line daytime mean pressures dropped by 13% from 96 to 84 mm Hg, and high line pressures dropped by 7% from 96 to 89 mm Hg.

Discussion

Our results confirm that through selective breeding and rigorous BP measurement, lines of baboons with significant differences in BP have been developed and that 32% to 46% of the variability was due to genetic factors. Our results are consistent with previous works that have demonstrated the development of lines of animals with diverging levels of BP.3-5,10-13

Because we measured direct arterial pressure overnight in unrestrained, adolescent baboons, our results represent basal pressures. From our results comparing night and day pressures and from results published by McGill et al.,14 day pressures are significantly greater than night pressures. Our results suggest that day to night reductions in low line progeny BP and heart rate are greater than for high line progeny and may account for a portion of the line difference. We could not study the effects of age on BP because all measurements were taken on adolescent baboons about 44 months old. However, we would expect BP levels to increase with age if the trend in baboons is similar to that reported from studies in human and animal populations.11-17 Likewise, the absence of any difference between genders indicates that adolescent male and female baboons have similar BP levels.

Methods used to characterize the blood pressure of lines of nonhuman primates have varied. Other investigators have used ketamine to tranquilize or immobilize subjects and have measured daytime, indirect pressure.10,11 Daytime mean BP values of high and low line African green monkeys were 95±5.5 and 79±2.6 mm Hg; nighttime mean BP values of comparably aged, high and low lines of baboons were 95±13 and 86±8 mm Hg.

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Table 2. Ranking of Sire Sibships by Progeny Mean Systolic, Diastolic, and Mean Blood Pressures

<table>
<thead>
<tr>
<th>Sire</th>
<th>BP* (mm Hg)</th>
<th>n</th>
<th>Systolic BP averages (mm Hg)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systolic</td>
</tr>
<tr>
<td>High line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X3576</td>
<td>178/111 (132)</td>
<td>17</td>
<td>133±19</td>
</tr>
<tr>
<td>X1947</td>
<td>147/89 (107)</td>
<td>3</td>
<td>127±12</td>
</tr>
<tr>
<td>X3818</td>
<td>181/116 (136)</td>
<td>8</td>
<td>124±09</td>
</tr>
<tr>
<td>X2892</td>
<td>177/102 (126)</td>
<td>4</td>
<td>122±08</td>
</tr>
<tr>
<td>X2617</td>
<td>161/100 (119)</td>
<td>21</td>
<td>120±10</td>
</tr>
<tr>
<td>Low line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X808</td>
<td>121/58 (78)</td>
<td>3</td>
<td>115±08</td>
</tr>
<tr>
<td>X3314</td>
<td>123/68 (85)</td>
<td>14</td>
<td>114±07</td>
</tr>
<tr>
<td>X3162</td>
<td>138/79 (98)</td>
<td>30</td>
<td>113±10</td>
</tr>
</tbody>
</table>

BP, blood pressure; n, number of animals. Mean BP is in parentheses.

*Day BP measured under ketamine immobilization.

†Night BP measured with tether.
TABLE 3. Systolic, Diastolic, and Mean Blood Pressure and Heart Rates Measured During Night and Day of Baboons Selectively Bred for High and Low Blood Pressure

<table>
<thead>
<tr>
<th>Line</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Mean</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (n=7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night</td>
<td>125±0.7</td>
<td>64±0.8</td>
<td>89±0.8</td>
<td>77±13</td>
</tr>
<tr>
<td>Day</td>
<td>136±0.6</td>
<td>70±0.4</td>
<td>96±0.4</td>
<td>101±20</td>
</tr>
<tr>
<td>*p&lt;</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Low (n=6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night</td>
<td>117±0.8</td>
<td>60±0.5</td>
<td>84±0.3</td>
<td>74±10</td>
</tr>
<tr>
<td>Day</td>
<td>132±1.3</td>
<td>71±0.8</td>
<td>96±0.8</td>
<td>114±14</td>
</tr>
<tr>
<td>*p&lt;</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
</tr>
</tbody>
</table>

HR, heart rate; bpm, beats per minute; n, number of animals.
*Statistical significance of the differences between night and day pressures as indicated by the Wilcoxon Signed Rank test.

One of our objectives in developing these lines of baboons was to demonstrate that genetic factors affect BP regulation. Heritability was 0.46±0.19 for systolic and 0.32±0.18 for diastolic pressure; that is, genetic factors accounted for 46% of the variability in systolic and 32% of the variability in diastolic pressure. Because heritability estimates were computed using data from selectively bred animals, they are biased. However, these estimates are similar to those obtained in studies of humans. For example, Miall and Oldham suggested that 33-46% of the variation in systolic pressure in human populations could be explained by genetic factors. Heritability for genetically heterogeneous animal populations was estimated by Schlager to be 20%.

We have shown that genetic factors contribute to blood pressure control in baboons. By measuring blood pressure under ketamine immobilization and using positive assortative mating of extreme phenotypes, we developed sibships with high and low BP levels (Table 2). The clear ranking of sires by progeny mean values into high and low lines demonstrates the validity of our methods.

References
Selective breeding to develop lines of baboons with high and low blood pressure.
D Carey, C M Kammerer, R E Shade, K S Rice and H C McGill, Jr

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