Genetic Influences on Insulinemia in Normotensive Twins

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The aim of this study was to establish the corresponding heritability estimates were 0.54 for FPI and 0.66 for RIR. Adjusting for age, gender, and body mass index did not affect heritability estimates for either FPI or RIR. Our data indicate that genetic factors are important determinants of insulinemia in normal subjects, independent of body mass index.

The hypothesis that insulin resistance and compensatory hyperinsulinemia contribute to the pathogenesis of essential hypertension has gained enormous interest. In many investigations, be it epidemiological surveys or case-control studies, an association between some measure of plasma insulin (fasting level, single postglucose reading, sum of response values) and blood pressure has been reported. The strength of the association and its persistence after adjustment for age, gender, and obesity, however, have varied considerably, with some negative studies published.

Several articles have indicated that the relationship between insulin resistance and blood pressure has either a constitutional or a genetic basis. Normotensive offspring of hypertensive parents are insulin resistant and hyperinsulinemic, as compared with those of normotensive parents. Intrafamilial variance of insulin sensitivity is significantly lower than its interfamilial variance. The longitudinal observations in healthy subjects indicate that high fasting plasma insulin is a significant predictor of subsequent development of hypertension. The strength of the relation between insulinemia and blood pressure is significantly influenced by ethnic factors.

The aim of this study was to establish the contribution of genetic factors to the variance of plasma insulin concentration in healthy, normotensive twins.

METHODS

Subjects
A total of 34 pairs of twins were investigated: 11 female and six male pairs of monozygotic (MZ) twins, and 12 female and five male pairs of dizygotic (DZ) twins. The reported twin zygosities was confirmed using the PCR method, amplifying some highly discriminating micro- and minisatellite systems.
TABLE 1. CLINICAL CHARACTERISTICS OF THE STUDIED SUBJECTS

<table>
<thead>
<tr>
<th></th>
<th>MZ Twins</th>
<th>DZ Twins</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>19.4 (4.7)</td>
<td>21.5 (5.7)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.5 (2.6)</td>
<td>21.4 (2.4)</td>
<td>NS</td>
</tr>
<tr>
<td>24-h SBP (mm Hg)</td>
<td>117.1 (10.5)</td>
<td>114.4 (7.2)</td>
<td>NS</td>
</tr>
<tr>
<td>24-h DBP (mm Hg)</td>
<td>68.9 (5.1)</td>
<td>66.3 (6.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values presented as means (SD).
MZ, monozygotic; DZ, dizygotic.

TABLE 2. MEAN VALUES AND MEAN SQUARES OF FASTING PLASMA INSULIN AND RELATIVE INSULIN RESISTANCE

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Mean Squares</th>
<th>Test of Genetic Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MZ</td>
<td>DZ</td>
<td>Among-Pair</td>
</tr>
<tr>
<td>FPI (mU/L)</td>
<td>7.8</td>
<td>8.3</td>
<td>19.3</td>
</tr>
<tr>
<td>RIR</td>
<td>1.70</td>
<td>1.75</td>
<td>1.07</td>
</tr>
<tr>
<td>Adjusted for age, gender, and body mass index</td>
<td>7.9</td>
<td>8.6</td>
<td>16.0</td>
</tr>
<tr>
<td>FPI (mU/L)</td>
<td>1.73</td>
<td>1.85</td>
<td>0.94</td>
</tr>
<tr>
<td>RIR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MZ, monozygotic; DZ, dizygotic; FPI, fasting plasma insulin; RIR, relative insulin resistance.
TABLE 3. INTRACLASS CORRELATION COEFFICIENTS FOR FASTING PLASMA INSULIN AND RELATIVE INSULIN RESISTANCE

<table>
<thead>
<tr>
<th></th>
<th>MZ Intraclass r</th>
<th>DZ Intraclass r</th>
<th>Heritability G = 2(rMZ - rDZ)</th>
<th>Common Environment C = 2rDZ - rMZ</th>
<th>Residual S = 1 - G - C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted FPI</td>
<td>0.85</td>
<td>0.58</td>
<td>0.54</td>
<td>0.31</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>0.84</td>
<td>0.51</td>
<td>0.66</td>
<td>0.18</td>
<td>0.16</td>
</tr>
<tr>
<td>Adjusted for age, gender, and body mass index FPI</td>
<td>0.85</td>
<td>0.59</td>
<td>0.52</td>
<td>0.33</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>0.81</td>
<td>0.44</td>
<td>0.74</td>
<td>0.07</td>
<td>0.19</td>
</tr>
</tbody>
</table>

MZ, monozygotic; DZ, dizygotic; FPI, fasting plasma insulin; RIR, relative insulin resistance.

type. The link between insulin resistance and blood pressure is typically demonstrable in lean subjects, either normotensive or hypertensive, is heavily confounded by the presence of overweight, and shows an element of familial aggregation. Insulinemia and insulin resistance are more closely correlated with ambulatory blood pressure than with the commonly used office blood pressure. Several mechanisms have been proposed to explain the hypertensive effect of insulin, including the influence on renal sodium absorption, cation transport, proliferation of vascular smooth muscle cells, and the effects on the sympathetic nervous system. Ethnic differences, along with the longitudinal observations in normotensive individuals, prehypertensives, and in offspring of hypertensives, all point to an inherent link between insulin and blood pressure.

This study was conducted in young normotensive subjects, and the relevance of these findings to hypertension could not be examined. One limitation of this study is that we measured only fasting insulin levels, which are merely a crude measure of insulin resistance. However, since hypertension and other cardiovascular complications believed to be associated with hypertension and hyperinsulinemia are the result of chronic changes, it is likely that estimates of insulin resistance reflecting these long-term changes are most beneficial in understanding these diseases. A measure of insulin resistance that probably reflects long-term adaptations is the fasting plasma insulin concentration. Furthermore, the fasting insulin concentration and relative insulin resistance index in young normal subjects significantly correlate with other estimates of insulin resistance.

In summary, genetic factors are important determinants of insulinemia in normotensive subjects. The genetic variance for insulinemia remains significant after adjustment for body mass index. Our results support the concept of genetic origin of insulin resistance.

REFERENCES

5. Pollare T, Lithell H, Berne C: Insulin resistance is a


