Increased Resistance of Iron-Deficient Mice to Salmonella Infection

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Nutritional iron deficiency in mice attenuated Salmonella typhimurium infection compared with both iron-substituted littersmates and normal diet control animals.

Interaction between invading microorganisms and their hosts involves bacterial nutrition. One host defense mechanism aimed at microbial starvation appears to be limitation of iron supply (10, 13). Tight binding of the metal to transferrin reduces the amount of iron directly available to bacteria. This type of serum bacteriostasis is closely related to the degree of transferrin iron saturation (4).

In this study, the susceptibility to Salmonella typhimurium (2386/74) infection was examined in three groups of NMRI mice as follows: (A) weaning animals, examined for iron deficiency by being fed a commercial diet containing less than 5 mg of iron per kg; (B) littersmates identically housed and fed, but given an intraperitoneal injection of 1 to 1.5 mg of iron as iron dextrin 10 to 14 days before infection; and (C) mice of identical sex and age receiving a stock diet containing 360 mg of iron per kg. The animals were intraperitoneally infected with 90 to 150 viable organisms, and daily deaths were recorded for 4 weeks. The microorganisms were stored at -40°C. Inoculation was preceded by subsequent cultivations on blood agar (24 h) and DST (Oxoid) slant agar (18 h). Bacterial suspensions in Isoton (Coulter Electronics) were counted with a Coulter Counter, and the injection volume was adapted to 0.5 ml of saline. Five mice of each group were sacrificed at the time of infection for hemoglobin, serum iron, and total iron-binding capacity measurements by standard methods adapted to microtechniques (3, 6). For whole-body iron assay, all mice were dissolved in nitric acid at the end of the study (Table 1).

Iron-deficient mice began to die later and at a lower rate than the controls (Fig. 1). Dietary differences exclude direct comparison between groups A and C. But, nutritional factors cannot explain the different survival patterns of groups A and B. Thus, iron substitution increased the mortality of iron-deficient animals. Also, no evidence exists that the high-iron diet was lacking

<table>
<thead>
<tr>
<th>Group</th>
<th>Mice (no. infected)</th>
<th>Hemoglobin (g/100 ml)</th>
<th>Serum iron (µg/100 ml)</th>
<th>Total iron-binding capacity (µg/100 ml)</th>
<th>Whole-body iron (µg/animal)</th>
<th>Surviving animals (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low-iron diet</td>
<td>10.0 ± 2.0 (P &lt; 0.001)*</td>
<td>116 ± 76 (P &lt; 0.001)*</td>
<td>601 ± 101 (P &lt; 0.001)*</td>
<td>1,180 ± 310 (P &lt; 0.001)*</td>
<td>58.5</td>
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<tr>
<td></td>
<td>(15, 15, 15, 26)</td>
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<tr>
<td>B</td>
<td>Low-iron diet plus parenteral iron</td>
<td>11.7 ± 0.9 (P &lt; 0.001)*</td>
<td>314 ± 77 (P &lt; 0.001)*</td>
<td>571 ± 113 (NS)*</td>
<td>1,714 ± 568 (P &lt; 0.001)*</td>
<td>19.7</td>
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<tr>
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<td>(17, 17, 11, 14)</td>
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<tr>
<td>C</td>
<td>Normal diet</td>
<td>12.8 ± 1.0 (NS)*</td>
<td>330 ± 152 (NS)*</td>
<td>409 ± 31 (NS)*</td>
<td>1,639 ± 449 (NS)*</td>
<td>10.8</td>
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<tr>
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<td>(10, 10, 15, 20)</td>
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</table>

* Statistical evaluation between groups was done by Student’s t test.
* Statistical evaluation by the chi-square test.
* Average body weights of groups A, B, and C were not significantly different.
* Group A to group C.
* Group A to group B. NS, Not significant.
* Group B to group C. NS, Not significant.
Mean transferrin saturation ([serum iron/total iron-binding capacity] × 100) was 80 and 20% in mice receiving the stock diet and in anemic animals, respectively; the intermediate value in the iron-substituted group must be ascribed to the short time elapsing between iron injection and investigation. The moderate degree of the deficiency state may have been a circumstance underlying the greater fitness of the animals fed a low-iron diet. Comparative evaluation of variable degrees of severity of iron deficiency might point to a subtle balance in which various components of host defense are affected in opposite ways by the lack of iron (1, 5, 11).

We suggest that the result obtained in this study is the consequence of competition for iron. On the host's side, other iron-binding proteins besides transferrin might be involved. Some findings suggest a synergistic action of iron-binding proteins and specific antibodies (2, 9). Microbial iron acquisition, on the other hand, depends on specific iron transport systems, whose efficiency partly determines virulence (7, 8, 12). Further work, besides examination of other host-pathogen combinations, must consider a greater number of variables.

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LITERATURE CITED