EDITORIAL

L-Dopa and Favism

By E. Beutler

Favism is an acute hemolytic anemia which occurs in glucose-6-phosphate dehydrogenase-deficient subjects when they ingest fava beans. Susceptibility to the hemolytic effect of fava beans appears to require some factor, possibly genetic in nature, in addition to glucose-6-phosphate dehydrogenase deficiency, since not all enzyme-deficient subjects develop hemolysis when they are exposed to the beans.

The nature of the hemolytic principle in fava beans has been the topic of considerable speculation, and several investigators have presented experimental data suggesting that various GSH-oxidizing compounds may be found in the beans. Furthermore the reason why only some G-6-PD deficient individuals develop hemolysis is not known.

Several investigators incubated G-6-PD-deficient red cells with a crude saline extract of fava beans and showed that such an extract could result in destruction of red cell GSH. Lin, and Mager et al. in fractionating fava beans believed that the active substances might be divicine and isouremil. The latter authors found that these substances, in a concentration of 2 μmoles/ml of incubation mixture, could destroy much of the GSH of G-6-PD-deficient cells, but not of normal red cells. Kosower and Kosower found that concentrations of L-Dopa as low as 0.75 μmoles/ml of incubation mixture could produce some loss of GSH from G-6-PD deficient cells. However Razin et al. failed to find an effect even when 10 μmoles of Dopa were added to each ml of reaction mixture. They suggested that Dopa or ascorbate might act synergistically with substances such as vicine or divicine. They also noted that alkali-treated Dopa was much more effective as an oxidant of GSH than native L-Dopa.

We now suggest that the active hemolytic principle from fava beans is dopaquinone and that susceptibility to the hemolytic effect of fava beans may depend upon the rate of its production from L-Dopa through the action of tyrosinase.

Our attention was first attracted to the possible role of L-Dopaquinone in the etiology of favism by the close analogy which exists between cataract
Table 1.—The Effect of Incubation With Dopa With and Without Tyrosinase on Red Cell GSH

<table>
<thead>
<tr>
<th>Dopa (μmoles/ml. final concentration)</th>
<th>Postincubation GSH (mg per cent)</th>
<th>G-6-PD-deficient</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GSH=37 mg per cent</td>
<td>GSH=50 mg per cent</td>
</tr>
<tr>
<td></td>
<td>0 Tyrosinase 0 Tyrosinase 0 Tyrosinase</td>
<td>0 Tyrosinase 0 Tyrosinase</td>
<td></td>
</tr>
<tr>
<td>0.152</td>
<td>36 24 40 46</td>
<td>0 Tyrosinase 0 Tyrosinase</td>
<td></td>
</tr>
<tr>
<td>0.076</td>
<td>31 24 48 46</td>
<td>0 Tyrosinase 0 Tyrosinase</td>
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</tr>
<tr>
<td>0.038</td>
<td>32 28 46 46</td>
<td>0 Tyrosinase 0 Tyrosinase</td>
<td></td>
</tr>
<tr>
<td>0.015</td>
<td>34 30 46 46</td>
<td>0 Tyrosinase 0 Tyrosinase</td>
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<tr>
<td>0.007</td>
<td>34 31 47 47</td>
<td>0 Tyrosinase 0 Tyrosinase</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>35 33 48 48</td>
<td>0 Tyrosinase 0 Tyrosinase</td>
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formation in the lens, on the one hand, and Heinz body formation in red cells in the course of drug-induced hemolysis on the other. Both the erythrocyte and the lens fibers are nonnucleated cells without a citric acid cycle. Both contain a highly specialized group of proteins which are precipitated under oxidative insult. Fava beans are the major source of large amounts of free L-Dopa, and are the source from which L-Dopa is produced commercially. Srivastava et al. had suggested that one of the pathogenic mechanisms of cataract formation might be the oxidation of tyrosine to dopaquinone through the action of the enzyme tyrosinase (Fig. 1).

We have therefore investigated the possible effect of this oxidation product of L-Dopa on the glutathione of normal and G-6-PD-deficient red blood cells. In order to convert L-Dopa into dopaquinone, 20 μl. of an L-Dopa solution were added to 50 μg. of mushroom tyrosinase (Sigma) in 5 μl. of water. 0.5 ml. of whole blood, collected in ACD solution, were added immediately. The samples were mixed briefly at the beginning of incubation at 37°C, and after 1 hour. After 2 hours, GSH determinations were carried out using the DTNB method. The results of a typical study are shown in Table 1. It is apparent that L-Dopa, at the relatively low concentrations employed, had no measurable effect on the GSH content of G-6-PD-deficient or normal cells. The addition of tyrosinase, however, converted the Dopa into a substance, presumably dopaquinone, which had the capacity to partially deplete G-6-PD-deficient red cells of GSH. Fava beans may contain 0.25 per cent of L-Dopa by weight, and distribution of the amount of Dopa which is present in 100 Gm. of fava beans in a 5 liter blood volume results in a concentration almost twice of the highest concentration used in these investigations, a concentration which resulted in destruction of about one-third of the GSH in G-6-PD-deficient red cells in 2 hours. Our investigations tend to support the findings of Razin et al. that L-Dopa alone has little or no effect on red
cell GSH levels. It seems possible that the Dopa preparation used by Kosower and Kosower may have been partially oxidized to dopaquinone.

If, indeed, dopaquinone is the active principle in fava bean-induced hemolysis, it may be possible to explain the fact that some G-6-PD-deficient individuals are susceptible to favism, while others are not. A polymorphism of the enzyme system required for the conversion of L-Dopa to dopaquinone, the tyrosinase system, could easily explain such individual differences. Unfortunately, we have been unable to detect tyrosinase activity in serum or peripheral blood cells, and the detection of such a polymorphism would, therefore, be very difficult. The differences in response to fava beans could also be due to differences in the rate of metabolism and elimination of dopaquinone formed from L-Dopa of the beans, or in the rate of decarboxylation of L-Dopa.

L-Dopa has recently gained a prominent place in the treatment of Parkinsonism. This provides a unique opportunity for a test of this hypothesis. If, indeed, L-Dopa is the factor in fava beans which produces hemolysis, some patients receiving L-Dopa should develop a hemolytic anemia, not of the Coombs-positive, α methyl dopa, type but of the same type seen in patients with favism. If, on the other hand, it can be shown that patients with Parkinsonism who have a history of favism, can ingest L-Dopa with impunity, the search for the hemolytic factor in fava beans will have to go on.

REFERENCES


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