The Respiratory Metabolism of Regenerating Rat Liver*

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Regenerating liver is commonly used as a source of rapidly growing tissue, since the maximum rate of growth of this tissue exceeds that of most tumors (1, 11). Generally, it has been considered that, in the case of regenerating liver, rapid tissue growth occurs at the expense of unchanged oxygen consumption or glycolysis and that the over-all metabolic patterns of resting adult and regenerating liver are essentially the same (8, 8). This concept arose apparently from a single report (14) concerning the respiratory metabolism of regenerating liver, in which it was concluded that partial hepatectomy had no effect on either the oxygen consumption or the glycolysis of rat liver.

The additional energy requirements associated with any rapid growth of a tissue must be satisfied either by an increase in tissue respiration or an increase in glycolysis. A tissue possessing adequate cytochrome reserve (17) could satisfy any additional energy requirements by an increased oxidation. In the case of the tumor, which is known to be deficient in the cytochrome system and hence possesses no oxidative reserve (9), the energy requirements are met by an increased glycolysis. It is known that there is a depression in a number of oxidative enzymes in the liver following partial hepatectomy. These enzymes include succinic dehydrogenase (15, 18), malic dehydrogenase, cytochrome reductase, oxalacetic oxidase (15), and glutamic dehydrogenase (7). On the other hand, Greenstein (10) and Shack (17) have reported that the cytochrome oxidase activity in regenerating liver at the time of maximum rate of liver growth, which occurs at about 72 hours after partial hepatectomy (11), were also determined.

MATERIALS AND METHODS

Male rats of the Yale-Wistar strain, which weighed from 140 to 200 gm. at the time of operation, were partially hepatectomized by the method of Higgins and Anderson (11). Clean, but not sterile, conditions were maintained. It was experimentally determined that 70.2 ± 0.5 per cent of the liver was removed at operation. This value is in good agreement with that reported by several other investigators (1, 11, 12). Normal rats and sham-operated rats, of the same age and sex as the experimental animals, served as controls. All animals were fed a diet of Purina Dog Checkers and were fasted for 24 hours prior to sacrifice. The animals were killed by cervical fracture, and the liver was quickly excised and kept ice-cold until it was taken for oxygen consumption measurements by the standard Warburg technic (19). Liver homogenates were assayed for succinic dehydrogenase and cytochrome oxidase by the method of Schneider and Potter (16). The liver homogenates were prepared by placing the liver in an all-plastic tissue mincer, consisting of a tube 50 mm. long and 19 mm. wide, with a disc on one end containing numerous holes about 1 mm. in diameter. The parenchyma was then forced through the holes with a tightly fitting hand-driven piston and collected in ice-cold water. Since only the liver parenchyma was assayed for succinic dehydrogenase and cytochrome oxidase, the normal values reported in the studies are somewhat greater than the values reported by Schneider and Potter for the whole liver (16).

RESULTS AND DISCUSSION

The oxygen consumption of liver slices from partially hepatectomized rats was higher than that...
of normal liver slices. This increase was significantly greater at 2, 7, 14, and 21 days after operation than the increase which resulted from sham operation. The values at the various time intervals after operation are shown in Table 1.

The increase in liver respiration at 24 hours after partial hepatectomy can be attributed probably to trauma caused by the operation, since an equal increase was observed in animals at 24 hours after sham operation. It has been shown by other investigators (4) that shock, induced by burning, freezing, or ischemia, causes the oxygen consumption of rat liver to increase 10–25 per cent above the normal value. The higher Qo₁'s at 2, 7, 14, and 21 days after partial hepatectomy cannot be due to trauma, however, since the respiration of the liver of the sham-operated animals had returned to near normal at these times. The data show that, although the Qo₁ at 72 hours after operation was considerably higher than the normal Qo₁, it was not different from that of the 72-hour sham-operated animals.

The over-all increase in liver respiration following partial hepatectomy undoubtedly reflects an increase in the oxidative metabolism of the liver to meet the additional energy requirements associated with rapid growth. Because maximum regenerative growth is supposed to occur at about 72 hours after partial hepatectomy, one might suspect that the maximum increase in oxygen consumption would also occur at this time if there were a relationship between the oxygen consumption and regeneration. The data presented here show that the maximum increase in oxygen consumption may have occurred at any time between 3 and 7 days, so that the maximum increase in respiration does not coincide with the maximum rate of regeneration.

Since liver regeneration is generally considered to be completed shortly after 14 days (1, 11) and was explanted and that, although resting liver of old rats failed to grow in such cultures, regenerating liver from the same animals grew fully as well as that from younger controls. This increase in proliferative capacity in old rats could still be demonstrated 45 days after partial hepatectomy, which was several weeks after regeneration was supposed to be complete. Although the original weight of the liver may be replaced within 14 days after partial hepatectomy, the observations of Glinos, and the data presented here showing that the increase in oxygen consumption persists for a long time after 14 days, demonstrate the fact that one cannot assume that the metabolism of "regenerated" liver is normal after 14 days.

Succinic dehydrogenase and cytochrome oxidase activities in the liver were markedly decreased at 48 and 72 hours after partial hepatectomy, while sham operation had no effect. These data are shown in Table 2. The depression of succinic dehydrogenase activity in the liver of the rat following partial hepatectomy is in agreement with

### TABLE 1

**OXYGEN CONSUMPTION OF LIVER SLICES FROM RATS AT VARIOUS TIMES AFTER SHAM OPERATION AND PARTIAL HEPATECTOMY**

<table>
<thead>
<tr>
<th>Time after operation</th>
<th>No. rats</th>
<th>Qo₁</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>9.5±0.2</td>
<td>0.001</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>9.9±0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>8.4±0.6</td>
<td>0.025</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>7.1±0.2</td>
<td>0.001</td>
</tr>
<tr>
<td>21</td>
<td>2</td>
<td>8.7±0.2</td>
<td>0.001</td>
</tr>
<tr>
<td>42</td>
<td>4</td>
<td>8.7±0.1</td>
<td>0.001</td>
</tr>
<tr>
<td>70</td>
<td>2</td>
<td>7.3±0.6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Normal liver Qo₁ = 7.5 ± 0.4.
† Probability that the difference between the Qo₁ of the partially hepatectomized animals and the Qo₁ of the sham-operated animals is due to chance alone.

Standard error of the mean.
the findings of other investigators (15), although in the present studies the per cent decrease was found to be greater. The liver cytochrome oxidase activity was found to be decreased after partial heptectomy, although Greenstein (10) and Shack (17) reported that there was no change in liver cytochrome oxidase activity 48 hours after operation. The fact that a larger per cent decrease in cytochrome oxidase activity 48 hours after operation is consistent with the reported depression in liver cytochrome oxidase following partial hepatectomy, since only the parenchyma was assayed for these enzymes. The decrease in cytochrome oxidase activity following partial heptectomy is consistent with the reported depression in the activities of other mitochondrial enzymes (7, 15, 18). Greenbaum et al. (7) postulated that the decrease in these mitochondrial enzymes following partial heptectomy was due to the fact that the mitochondria react more slowly to partial heptectomy than do other parts of the liver cell. Thus, the decrease in the activity of cytochrome oxidase in the regenerating liver could be due to a lag in the synthesis of this enzyme, since cytochrome oxidase has been found only in the mitochondria (13).

SUMMARY

1. The oxygen consumption of regenerating rat liver was significantly higher than that of normal liver or of liver from sham-operated animals. This increase lasted for more than 21 days following partial heptectomy.

2. Although the original weight of the liver may be replaced within 14 days after partial heptectomy, the metabolism of the "regenerated" liver is not normal for a long time after 14 days.

3. Succinic dehydrogenase and cytochrome oxidase activities were markedly decreased at 48 and 72 hours after partial heptectomy. Sham operation had no effect on the activity of these two enzymes in the liver.


REFERENCES


7. Greenbaum, A. L.; Greenwood, F. C.; and Harkness,

TABLE 2

<table>
<thead>
<tr>
<th>HOURS AFTER</th>
<th>SUCCHINIC DEHYDROGENASE</th>
<th>CYTOCHROME OXIDASE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rats</td>
<td>Qo</td>
</tr>
<tr>
<td>Control†</td>
<td>10</td>
<td>100±5.6</td>
</tr>
<tr>
<td>48</td>
<td>3</td>
<td>52±5.0</td>
</tr>
<tr>
<td>72</td>
<td>6</td>
<td>70±8.4</td>
</tr>
</tbody>
</table>

* Probability that the difference between the normal enzyme activity and that of the partially hepatectomized animals is due to chance alone.

† Normal plus sham-operated animals. Since sham operation had no effect on the activities of succinic dehydrogenase and cytochrome oxidase in the liver, the sham-operated animals were combined with the normal animals as controls.

‡ Standard error of the mean.
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