METABOLISM OF ACETATE BY THE EXTRAHEPATIC TISSUES*

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Acetic acid can be involved in several important metabolic processes. It has been shown to be a precursor of foodstuffs such as ketone bodies (1), fat (2, 3), and cholesterol (4). It has been estimated that acetate may be an intermediate for a large fraction of the total foodstuffs metabolized by the body (5, 6). This is difficult to verify, since the methods available for the chemical estimation of small amounts of acetic acid are inadequate. If there is a rapid turnover of the compound, the amount present in the body at any given time could be small. It would be of value to ascertain to what extent the extrahepatic tissues are capable of oxidizing acetate directly. Considerable amounts can be oxidized to carbon dioxide by the intact animal (7, 8). Since the liver is capable of chemically transforming acetic acid, it is not known to what extent the peripheral tissues use acetate, as such, and to what extent they utilize the chemical products resulting from the liver action.

Recent work has shown that at least two extrahepatic tissues, the heart (9) and the diaphragm (9, 10), are capable of oxidizing acetate to CO₂. We have investigated this problem by the use of C¹⁴-labeled acetate in the eviscerated animal. By removal of the liver and kidneys, the chief sites of transformation of acetate into intermediary products are undoubtedly eliminated and a preparation is obtained in which the direct utilization of acetate by the peripheral tissues can be studied.

EXPERIMENTAL

Treatment of Animals—Non-fasted rabbits weighing approximately 2 kilos were used. The abdominal viscera, including the kidneys, were removed by the method described by Mann (11). After recovery from the operation, which included the insertion of a tracheal cannula, the labeled acetate was injected intravenously and collection of the expired

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air was begun in order to follow the tagged CO₂ produced from the acetate. The activity injected was similar in all cases and was approximately 1.2 million counts contained in 1 mg. of acetate; some rabbits received only this, while others received various amounts of unlabeled acetate as carrier in addition.

Analytical Methods—The methods used for the collection of the expired CO₂ and the determination of its radioactivity have been described (12). In all cases the samples used for the radioactive determinations were of infinite thickness.

The acetate-2-C¹⁴ (1 mc. in 1 mm) was purchased from Tracerlab, Inc., as the sodium salt.

Results

Manner in Which C¹⁴O₂ Is Eliminated—Table I shows the specific activities of the expired CO₂ of the successive periods for the different animals. It is noted that the specific activity of the expired CO₂ reached a maximum either in the 1st or in the 2nd hour, depending somewhat on the amount of carrier acetate that was administered. From the specific activity of the expired CO₂ one may derive a good idea of the manner in which the tagged CO₂ was produced by the tissues. At first the expired CO₂ had a lower specific activity than that produced by the cells, since at the beginning of the experiment there was a considerable amount of untagged "body" CO₂ which diluted the active material resulting from metabolism. The amount of this "body" CO₂ equaled that which was expired in about 30 minutes (13). The fact that the specific activity of the expired CO₂ reached a maximum so early suggests that the cells produced CO₂ of high activity from the beginning, but, as time went on, gave off CO₂ of lower and lower specific activities. After the maximum for the expired CO₂ had been reached, the CO₂ produced by the cells had a lower specific activity than that of the "body" CO₂ and hence diluted it. By the end of the 3rd hour, in almost all cases, the specific activity of expired CO₂ had dropped considerably from the peak; thus relatively little radioactivity remained in the body bicarbonate. The oxidation of acetate was largely completed by the end of the 3rd hour.

Effect of Added Carrier on Amount of Acetate Oxidized—Fig. 1 shows that the rate of oxidation of acetate was dependent upon its concentration in the body fluids. The total amount oxidized by the end of the 4th hour was roughly proportional to the amount of carrier acetate given. Although there was considerable variation among rabbits given the same dose of carrier, the animals receiving the largest dose of carrier oxidized as much of the labeled acetate to CO₂ as did those receiving the smaller doses.
TABLE I

Relative Specific Activities of Expired CO₂ after Acetate Administration

<table>
<thead>
<tr>
<th>Period of experiment, hrs.</th>
<th>Relative specific activity*</th>
<th>Acetic acid† administered, mg. per kilo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Experiment No.</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>0 -0.5</td>
<td>868</td>
<td>715</td>
</tr>
<tr>
<td>0.5-1</td>
<td>605</td>
<td>770</td>
</tr>
<tr>
<td>1 -1.5</td>
<td>410</td>
<td>640</td>
</tr>
<tr>
<td>1.5-2</td>
<td>296</td>
<td>480</td>
</tr>
<tr>
<td>3</td>
<td>215</td>
<td>306</td>
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<td>4</td>
<td>150</td>
<td>175</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>106</td>
</tr>
</tbody>
</table>

Recovery of injected C¹⁴, %... 47 61 32 68 54 48 70 64 53 56 69 55 47

* Relative specific activity is the counts per minute per mg. of carbon.
† The carrier acetic acid was administered as the Na salt.

Fig. 1. Acetic acid oxidation as influenced by its concentration. The curves indicating the injected quantities of acetic acid (200 mg. per kilo, 300 mg. per kilo, etc.) represent Experiments 8 to 13 as given in Table I.
It is apparent that the oxidation of the acetate must reach a maximal rate very soon after the injection of the material. At the time the specific activity of the expired CO$_2$ showed a maximal value, the specific activity of the CO$_2$ produced by the cells must have decreased below a previous higher value. In our results that point was usually reached during the second or third half-hour period. The "body" CO$_2$ had to be equilibrated with the new tagged CO$_2$ during the preceding time and, therefore, required a high rate of production of labeled CO$_2$ during that time. During the period showing the peak of CO$_2$ specific activity, production of labeled CO$_2$ was probably close to the rate at which it was expired by the lungs. The rate of oxidation of acetic acid at that time could be calculated, since the proportion of acetate oxidized to the amount injected was given by the ratio of activity exhaled to activity injected. The average figure so obtained for the animal, as shown in Experiment 11, which received 800 mg. per kilo of carrier acetate, indicates that this rabbit was burning about 290 mg. of acetic acid per kilo per hour. This rate of acetate oxidation accounts for one-half of the total CO$_2$ expired in that period.

Our results cannot be used to settle the question as to whether there is normally a high basic turnover of acetate in metabolism. If such is the case, however, we can conclude that from the effect of added carrier on the rate of oxidation of the tagged material this "metabolic" acetate does not exchange with extracellular or injected acetate. We would expect that, if this intracellular "metabolic" acetate exchanged with the extracellular, when this was highly diluted with carrier, the specific activity of the intracellular acetate and of the CO$_2$ metabolized from it would be low. When the labeled acetate in the extracellular compartment is undiluted, the intracellular "metabolic" acetate would, in exchanging with it, attain a high specific activity and impart this to the produced carbon dioxide.

It is to be noted that the recovery after 5 hours was still far from the 100 per cent that was injected. At that time there remained in the body a large fraction (30 to 40 per cent) of the radioactive carbon that had been injected and yet very little radioactive carbon dioxide was exhaled at that time. The ratio of labeled to unlabeled carbon dioxide in the body was much lower than that immediately after injection of the acetate. This marked drop in specific activity of CO$_2$ occurred despite the fact that a large fraction of the injected acetate still remained in the body. This strongly suggests that the acetate had been changed to other compounds by the extrahepatic tissues. These compounds would appear to have had a much lower rate of oxidation to carbon dioxide than acetate.
SUMMARY

The oxidation of acetate by the extrahepatic tissues has been studied with the aid of C\textsuperscript{14}-labeled acetate. This compound is very rapidly oxidized to carbon dioxide by the eviscerated animal.

The amount of acetate oxidized in a given period is proportional to the amount injected and indicates that the rate of oxidation of this substance is proportional to its concentration in the animal.

The general tissues of the body have a high potential capacity to oxidize acetate which can be evoked by administering a large injection. Probably at least half the energy needs of the tissues can be supplied in this manner.

A considerable fraction (30 to 40 per cent) of administered acetate appears to be converted into other forms by the eviscerated animal.

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