PYRUVATE AND $\alpha$-KETOGLUTARATE METABOLISM IN THIAMINE DEFICIENCY*

BY RITA C. WRIGHT AND E. M. SCOTT

(From the Arctic Health Research Center, United States Public Health Service, Anchorage, Alaska)

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One obvious explanation for the effect of high fat diets in lowering the requirement for thiamine has been that fat metabolism does not require thiamine, while carbohydrate metabolism does. This explanation finds considerable support in one of the known functions of thiamine pyrophosphate. According to current theory, carbohydrate is oxidized to pyruvate, and pyruvate must be decarboxylated for further oxidation by way of the citric acid cycle. Fatty acids, on the other hand, are oxidized to form a 2-carbon compound and can undergo further oxidation in the citric acid cycle without a decarboxylation step. Since thiamine pyrophosphate is necessary for oxidation of pyruvate, probably in the decarboxylation step, thiamine-deficient animals might be able to maintain a more nearly normal metabolism on a diet high in fat.

If this explanation is correct, thiamine deficiency should not affect to any great extent other metabolic reactions in which fat is involved. According to present knowledge, however, thiamine pyrophosphate is a coenzyme for $\alpha$-ketoglutarate metabolism (1-4), and fat requires for its complete metabolism the oxidation of $\alpha$-ketoglutarate as an intermediate step.

The present experiments compare the effects of thiamine deficiency on $\alpha$-ketoglutarate oxidation and on pyruvate oxidation. The results are in accord with the concept that the effect of high fat diets on thiamine deficiency is due to the maintenance of a more nearly normal metabolism.

**Methods**

**Animals**—Weanling rats were fed one of two diets: normal diet, 24 per cent casein (vitamin-free), 20 per cent fat (hydrogenated vegetable oil), 4 per cent salt mixture (5), and 52 per cent sucrose; high fat diet, 60.5 per cent fat, 34 per cent casein, and 5.5 per cent salt mixture. Enzyme preparations from the animals on a high fat diet did not differ in properties from those on the normal diet, but the animals on the high fat diet were larger and lived longer. Vitamins were fed separately as pills five times

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725
weekly. Each pill contained 150 γ of riboflavin, 150 γ of pyridoxine hydrochloride, 250 γ of calcium pantothenate, 10 mg. of choline chloride, 0.5 mg. of niacin, 0.5 mg. of p-aminobenzoic acid, 2.5 mg. of inositol, 5 γ of biotin, 5 γ of folic acid, 100 γ of menadione, 0.05 γ of vitamin B₁₂, 1 mg. of α-tocopherol, 65 i.u. of vitamin A, and 13 i.u. of vitamin D. Normal animals received a pill containing, in addition to the above, 50 γ of thiamine hydrochloride. After 3 to 6 weeks on the diets, the tissues of a normal and of a deficient animal of the same age were tested for enzymatic activity.

Homogenates—Whole homogenates were prepared in 9 volumes of isotonic potassium chloride. Washed homogenates were prepared by disintegration in 9 volumes of isotonic sucrose, followed by centrifugation at 600 X g for 10 minutes. The supernatant fluid was decanted, made 0.04 M with magnesium chloride, and centrifuged for 10 minutes at 2200 X g. The precipitate was twice resuspended in 0.04 M magnesium chloride and reprecipitated by centrifuging at 2200 X g for 5 minutes.

Oxygen Uptake—With whole homogenates, each Warburg flask contained 0.4 ml. of 10 per cent homogenate, 9 X 10⁻⁶ M cytochrome c, 0.002 M adenosinetriphosphate, 2.5 X 10⁻⁴ M diphosphopyridine nucleotide (side arm), 0.01 M nicotinamide, 0.01 M potassium bicarbonate, 0.01 M magnesium chloride, 0.01 M potassium phosphate buffer (pH 7.35), 0.033 M potassium chloride, and 0.0167 M sodium pyruvate or α-ketoglutarate. The bath temperature was 30°. Substrate and enzyme were equilibrated together, the side arm was tipped in at zero time, and readings were taken for 30 minutes.

With washed homogenates, each flask contained homogenate (0.2 to 0.6 mg. of nitrogen per ml.), 3 X 10⁻⁶ M cytochrome c, 0.002 M adenosinetriphosphate, 1.0 X 10⁻⁴ M diphosphopyridine nucleotide, 0.01 M nicotinamide, 0.01 M potassium bicarbonate, 2.7 X 10⁻³ M magnesium chloride, 0.033 M potassium phosphate buffer (pH 7.35), and 0.0167 M substrate. The bath temperature was 30°. All components were equilibrated together for 10 minutes, and readings were taken for 30 minutes. Oxygen uptakes in the absence of substrate were subtracted from those obtained with substrate, although the former were usually negligible.

Results

The effects of thiamine deficiency and thiamine pyrophosphate supplementation on tissue homogenates are shown in Table I. In general, oxygen uptake was lowered by thiamine deficiency, the greatest decrease occurring in the presence of pyruvate. Added thiamine pyrophosphate had no appreciable effect on normal tissue homogenates except in one case. With deficient animals, thiamine pyrophosphate increased oxidation by
### Table I

**Oxygen Uptake of Whole Tissue Homogenates of Normal and Thiamine-Deficient Animals**

In the (b) experiments, the flasks contained 0.03 M malonate and the temperature was 38°; otherwise, conditions were as described in the text. Thiamine pyrophosphate (TPP) concentration, 3 × 10⁻⁴ M.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Liver (a)</th>
<th>Liver (b)</th>
<th>Kidney (a)</th>
<th>Kidney (b)</th>
<th>Heart (a)</th>
<th>Heart (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>O₂ uptake, normal tissues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3110</td>
<td>2400</td>
<td>4120</td>
<td>1760</td>
<td>3950</td>
<td>1140</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>3200</td>
<td></td>
<td>3490</td>
<td></td>
<td>2110</td>
<td></td>
</tr>
<tr>
<td>α-Ketoglutarate</td>
<td>4200</td>
<td>1880</td>
<td>7810</td>
<td>3340</td>
<td>5810</td>
<td>1680</td>
</tr>
<tr>
<td><strong>O₂ uptake, deficient tissues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>77 ± 16</td>
<td>77 ± 4</td>
<td>77 ± 12</td>
<td>85 ± 16</td>
<td>78 ± 17</td>
<td>103 ± 26</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>56 ± 7</td>
<td></td>
<td>67 ± 14</td>
<td></td>
<td>68 ± 34</td>
<td></td>
</tr>
<tr>
<td>α-Ketoglutarate</td>
<td>87 ± 7</td>
<td>67 ± 6</td>
<td>79 ± 8</td>
<td>62 ± 13</td>
<td>72 ± 19</td>
<td>78 ± 15</td>
</tr>
<tr>
<td><strong>Effect of TPP on normal tissues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>-5 ± 3</td>
<td>3 ± 4</td>
<td>8 ± 2</td>
<td>1 ± 2</td>
<td>9 ± 9</td>
<td>7 ± 12</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>4 ± 3</td>
<td></td>
<td>-5 ± 6</td>
<td></td>
<td>-6 ± 13</td>
<td></td>
</tr>
<tr>
<td>α-Ketoglutarate</td>
<td>2 ± 2</td>
<td>5 ± 3</td>
<td>10 ± 7</td>
<td>-17 ± 8</td>
<td>18 ± 2</td>
<td>3 ± 7</td>
</tr>
<tr>
<td><strong>Effect of TPP on deficient tissues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3 ± 3</td>
<td>6 ± 5</td>
<td>43 ± 10</td>
<td>13 ± 9</td>
<td>-13 ± 10</td>
<td>3 ± 4</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>40 ± 5</td>
<td>62 ± 4</td>
<td>11 ± 13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Ketoglutarate</td>
<td>11 ± 3</td>
<td>-2 ± 3</td>
<td>50 ± 4</td>
<td>1 ± 2</td>
<td>26 ± 11</td>
<td>-8 ± 3</td>
</tr>
<tr>
<td><strong>No. of determinations</strong></td>
<td>20</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

* *Microliters of oxygen per hour per 10 ml. of 10 per cent homogenate.

† Mean and standard error of the mean, expressed as per cent of normal tissue.

‡ Increase (positive) or decrease in oxygen uptake with added TPP over oxygen uptake in absence of TPP, expressed as per cent of oxygen uptake of normal tissue in absence of TPP.
liver in the presence of pyruvate, but had no effect on endogenous oxidation or on oxidation in the presence of \( \alpha \)-ketoglutarate. With kidney homogenates, all three oxidations were increased by the added coenzyme. The greatest increase in oxidation occurred in the presence of pyruvate, while the increase with \( \alpha \)-ketoglutarate was not significantly greater than that with no substrate. Oxidation in the presence of \( \alpha \)-ketoglutarate was increased by added thiamine pyrophosphate to about the same extent in homogenates of both normal and deficient heart.

Because of the magnitude of endogenous oxygen uptake in whole homogenates, it was believed that more conclusive results might be obtained with washed homogenates. These were prepared from liver and tested with a number of substrates, as shown in Table II. The oxidation of pyruvate and two substrates closely associated with pyruvate was decreased by deficiency, and only the oxidation of these was increased by thiamine pyrophosphate. Since the equilibrium of the lactate-pyruvate-lactic dehydrogenase system favors lactate, further oxidation of pyruvate

### Table II

Oxygen Uptake of Washed Liver Homogenates of Normal and Thiamine Deficient Animals

<table>
<thead>
<tr>
<th>Substrate</th>
<th>( Q_2 \text{ uptake, normal tissues, } Q_{22} (N)^* )</th>
<th>( Q_2 \text{ uptake, deficient tissues} )</th>
<th>Effect of TPP on normal tissues</th>
<th>Effect of TPP on deficient tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>per cent of normal</td>
<td>per cent of normal</td>
<td>per cent of normal</td>
<td>per cent of normal</td>
</tr>
<tr>
<td>( \alpha )-Ketoglutarate</td>
<td>125</td>
<td>92 ( \pm ) 9</td>
<td>(-6 \pm 6)</td>
<td>(5 \pm 6)</td>
</tr>
<tr>
<td>L-Malate</td>
<td>124</td>
<td>90 ( \pm ) 9</td>
<td>(2 \pm 4)</td>
<td>(5 \pm 5)</td>
</tr>
<tr>
<td>Oxalacetate</td>
<td>72</td>
<td>13 ( \pm ) 18</td>
<td>(69 \pm 31)</td>
<td>(129 \pm 20)</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>134</td>
<td>31 ( \pm ) 5</td>
<td>(-8 \pm 5)</td>
<td>(50 \pm 4)</td>
</tr>
<tr>
<td>( dl )-Lactate</td>
<td>125</td>
<td>60 ( \pm ) 10</td>
<td>(1 \pm 5)</td>
<td>(41 \pm 7)</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>97</td>
<td>83 ( \pm ) 10</td>
<td>(3 \pm 7)</td>
<td>(10 \pm 7)</td>
</tr>
<tr>
<td>Octanoate§</td>
<td>170</td>
<td>95 ( \pm ) 11</td>
<td>(-13 \pm 5)</td>
<td>(-8 \pm 9)</td>
</tr>
<tr>
<td>L-Proline</td>
<td>157</td>
<td>128 ( \pm ) 13</td>
<td>(1 \pm 6)</td>
<td>(-3 \pm 7)</td>
</tr>
<tr>
<td>L-Glutamate</td>
<td>195</td>
<td>118 ( \pm ) 9</td>
<td>(4 \pm 4)</td>
<td>(-7 \pm 4)</td>
</tr>
<tr>
<td>Succinate</td>
<td></td>
<td></td>
<td>386</td>
<td>125 ( \pm ) 10</td>
</tr>
<tr>
<td>Citrate</td>
<td>125</td>
<td>98 ( \pm ) 16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Microliters of oxygen per hour per mg. nitrogen.
† Mean and standard error of the mean of ten determinations.
‡ Five determinations. Increase (positive) or decrease in oxygen uptake produced by adding TPP, expressed as per cent of oxygen uptake of normal washed liver homogenate.
§ Substrate concentration, \(6.7 \times 10^{-4}\) M.
‖ Each flask contained phosphate buffer \(0.933\) M, cytochrome \(c\) \(3 \times 10^{-6}\) M, succinate \(0.0167\) M, and homogenate 0.1 to 0.3 mg. of N per ml.
is necessary for optimal oxidation of lactate. Oxalacetate must be de-
carboxylated to pyruvate, and the latter oxidized, before oxygen uptake is
observed with this substrate. However, oxalacetate resulting from malate
oxidation was apparently decarboxylated or oxidized so rapidly that it
did not inhibit malate oxidation. Oxalacetate oxidation by normal liver
homogenates was increased by added thiamine pyrophosphate.

The results of a more extended series of experiments with liver and other
tissues are presented in Table III. In all tissues except brain, thiamine
deficiency resulted in decreased pyruvate oxidation, which was stimulated
by added thiamine pyrophosphate. Oxidation of \( \alpha \)-ketoglutarate was low
in all cases except in brain, and did not respond to added thiamine pyro-
phosphate. Actually, however, the coenzyme did activate \( \alpha \)-ketoglutarate
oxidation by both normal and deficient liver tissues. Sanadi et al. have
found an activation of \( \alpha \)-ketoglutaric dehydrogenase by thiamine pyro-
phosphate, which they suggested was non-specific, since it could only be
demonstrated by one of three methods of determination (3). If activation
by thiamine pyrophosphate of \( \alpha \)-ketoglutarate oxidation in washed liver
homogenates was calculated as the per cent increase instead of per cent of
normal oxygen uptake, normal liver was activated 18 per cent and deficient

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{Substrate} & \text{Liver} & \text{Kidney} & \text{Heart} & \text{Brain} \\
\hline
\text{Pyruvate} & 145 & 51 & 838 & 183 \\
\alpha-Ketoglutarate & 161 & 280 & 399 & 129 \\
\hline
\text{Pyruvate} & 30 \pm 9 & 29 \pm 23 & 48 \pm 23 & 83 \pm 8 \\
\alpha-Ketoglutarate & 55 \pm 8 & 52 \pm 29 & 63 \pm 32 & 92 \pm 8 \\
\hline
\text{Pyruvate} & -7 \pm 4 & 87 \pm 46 & 6 \pm 6 & -3 \pm 7 \\
\alpha-Ketoglutarate & 18 \pm 4 & 7 \pm 10 & 22 \pm 14 & -1 \pm 4 \\
\hline
\text{Pyruvate} & 39 \pm 4 & 142 \pm 54 & 24 \pm 7 & -3 \pm 3 \\
\alpha-Ketoglutarate & 10 \pm 2 & 24 \pm 6 & -11 \pm 11 & -4 \pm 4 \\
\hline
\text{No. of determinations} & 20 & 5 & 5 & 5 \\
\hline
\end{array}
\]

* Increase (positive) or decrease in oxygen uptake produced by adding TPP to
the washed homogenate, expressed as per cent of oxygen uptake of normal washed
homogenates.
**TABLE IV**

Oxidation of Lactate and Pyruvate by Washed Liver Homogenates of Thiamine Deficient Rats

| Substrate                | Qₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒ{o} | Qₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒₒ.GetObjectImage
liver 19 per cent by thiamine pyrophosphate. Since on this basis thiamine pyrophosphate activated α-ketoglutarate oxidation by both normal and thiamine-deficient animals to the same extent, the non-specific nature of this activation seems confirmed.

The enzyme systems used in these studies contain active lactic dehydrogenase, and, because the lactate-pyruvate-dehydrogenase equilibrium favors lactate, added pyruvate disproportionates to a considerable extent. It was thought possible that this might make pyruvate appear more sensitive to thiamine deficiency than α-ketoglutarate is. The results in Table IV indicate that disproportionation does occur with pyruvate, tending to decrease oxygen uptake by pyruvate in the absence of thiamine pyrophosphate. However, there is still a marked effect of thiamine pyrophosphate with lactate alone or pyruvate plus lactate, and consequently the difference between the effects of thiamine pyrophosphate on pyruvate and α-ketoglutarate oxidation must have another explanation.
A study was made of the time-course of thiamine pyrophosphate activation of washed homogenates with pyruvate and α-ketoglutarate. As shown in Fig. 1, there was no appreciable lag period in either oxidation. Consequently, any combination of thiamine pyrophosphate and enzyme, if it occurred, must have been very rapid.

The effects of thiamine pyrophosphate concentration on washed homogenates of rat liver are presented in Fig. 2. The results suggest a dissociation equilibrium, but, because of disproportionation, it was not possible to calculate a Michaelis constant for the dissociation.

**DISCUSSION**

The above results show that the effects of thiamine deficiency on pyruvate oxidation and on α-ketoglutarate oxidation are different. Using thiamine-deficient animals, we have been unable to obtain evidence that thiamine pyrophosphate is a coenzyme of α-ketoglutarate oxidation. Previous results indicating that thiamine pyrophosphate is required for α-ketoglutarate oxidation are as follows: Barron et al. found that this coenzyme stimulated α-ketoglutarate oxidation by thiamine-deficient tissues (1). While we could not confirm this by our methods, it may have been, as these authors cautioned, because our animals were not sufficiently deficient. Stumpf, Zarudnaya, and Green reported a thiamine pyrophosphate-dependent α-ketoglutaric oxidase (2). While the α-ketoglutaric oxidase of Sanadi et al. was stimulated by thiamine pyrophosphate by only one method of determination, and consequently this was considered a non-specific activation, the purified enzyme contained bound thiamine pyrophosphate (3). Reed and DeBusk have reported a thiamine pyrophosphate-lipoic acid conjugate to be necessary for α-ketoglutarate oxidation in bacterial cells (4).

To explain the difference between pyruvate and α-ketoglutarate oxidation in thiamine deficiency, it might be assumed that thiamine pyrophosphate was much more tightly bound by α-ketoglutaric dehydrogenase than by pyruvic dehydrogenase. It is known that in extreme thiamine deficiency not all thiamine or thiamine pyrophosphate is depleted from the tissues (6). The fraction that remains might be associated with α-ketoglutaric dehydrogenase, while the more easily depleted portion could be associated with pyruvic dehydrogenase.

Another possible explanation for the difference in thiamine pyrophosphate requirement for pyruvate and α-ketoglutarate oxidation in thiamine deficiencies may be a difference in what constitutes the rate-limiting step in the two oxidations. The limiting step in pyruvic dehydrogenase in these studies is the thiamine pyrophosphate要求ing step. In α-ketoglutaric dehydrogenase, the system catalyzing the thiamine pyrophosphate-
requiring step may be in great excess, and hence the effects of deficiency of
thiamine pyrophosphate cannot be demonstrated because another step
limits the rate of oxygen uptake.

Regardless of the mechanism, pyruvate oxidation is more depressed in
thiamine deficiency than is α-ketoglutarate oxidation. This is consistent
with the view that fat in the diet alleviates the symptoms of thiamine
deficiency by allowing a more nearly normal metabolism, since fat by-
passes the oxidation of pyruvate.

**SUMMARY**

In thiamine-deficient tissues of rats, oxidation of pyruvate is depressed,
and it can be stimulated by addition of thiamine pyrophosphate. In the
same tissues, oxidation of α-ketoglutarate is not so greatly lowered, and
specific stimulation by addition of thiamine pyrophosphate could not be
demonstrated.

These results are consistent with the view that fat in the diet alleviates
the symptoms of thiamine deficiency by allowing more nearly normal
metabolism, since the oxidation of fat, unlike that of carbohydrate, by-
passes the oxidation of pyruvate.

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