Acetyl Coenzyme A Carboxylase

THE EFFECTS OF BIOTIN DEFICIENCY ON ENZYME IN RAT LIVER AND ADIPOSE TISSUE*

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SUMMARY

Feeding a low fat, biotin-deficient diet to young rats for 1 to 2 weeks leads to a decrease in acetyl coenzyme A carboxylase levels in epididymal adipose tissue with accumulation of the apoenzyme. These changes occur prior to changes in hepatic propionyl coenzyme A carboxylase levels. Acetyl coenzyme A carboxylase levels in liver decrease minimally with biotin deficiency, and little apoenzyme accumulates.

The presence of apoenzyme in adipose tissue of deficient rats was initially suggested by the rapid rise in acetyl coenzyme A carboxylase activity which occurred within minutes of biotin injection. Further evidence for the presence of apoenzyme in deficient adipose tissue came from equivalence point determinations with the use of an antibody against acetyl coenzyme A carboxylase. These experiments indicated that adipose tissue from deficient rats contains immunologically reactive but catalytically inactive protein which is presumably acetyl coenzyme A apocarboxylase.

Biotin-deficient and control rats were injected with 3H-biotin, and subsequently acetyl coenzyme A carboxylase was isolated from liver and adipose tissue by immunological precipitation. There was increased 3H-biotin incorporation into deficient adipose tissue enzyme compared with control adipose tissue enzyme but only minimally increased incorporation into liver enzyme, again demonstrating the marked difference in the metabolism of the enzyme in these tissues.

The conversion of acetyl coenzyme A apocarboxylase to holoenzyme was demonstrated in vitro with the use of a 105,000 X g supernatant fraction from adipose tissue of deficient animals. The marked change in activity of this enzyme in liver that follows dietary alterations has recently been shown to result from changes in the rates of synthesis and degradation of enzyme. Thus, deprivation of food results in both decreased synthesis of acetyl-CoA carboxylase in liver and increased degradation of enzyme. Alternatively, feeding a low fat diet increases the rate of synthesis of acetyl-CoA carboxylase 5- to 10-fold over rates seen in fasted animals, with a return of degradation rates to those seen in animals fed a normal (Purina rat chow) diet.

Early attempts to demonstrate decreased acetyl-CoA carboxylase activity in livers of biotin-deficient rats were unsuccessful (4, 5). Recently, Dakshinamurti and Desjardins, using a low fat diet to increase the biosynthesis of acetyl-CoA carboxylase, have demonstrated decreased acetyl-CoA carboxylase activity in liver and adipose tissue from biotin-deficient animals compared with similarly fed nondeficient animals (6). These authors demonstrated a 50% decrease in acetyl-CoA carboxylase activity in liver after 6 to 8 weeks of biotin deprivation, with a more striking 6-fold decrease in enzyme activity in adipose tissue. The difference in response of these tissues to biotin deficiency was further shown by the minimal changes in total liver lipid content, compared with a 2- to 3-fold decrease in adipose tissue lipid content.

In the present studies, we have further demonstrated this marked difference between the response of liver and adipose tissue to biotin deprivation by demonstrating a 3-fold decrease in adipose tissue acetyl-CoA carboxylase activity after only 7 to 14 days of biotin deprivation, at which time no significant decrease in liver enzyme activity was seen. We have demonstrated the accumulation of acetyl-CoA apocarboxylase in adipose tissue but not in liver of these animals.

We have also demonstrated the conversion of acetyl-CoA apocarboxylase to the holoenzyme in adipose tissue both in vivo and in vitro, using extracts of epididymal fat pad.

METHODS

Animals and Diets—Young male Sprague-Dawley rats (50 to 75 g) were used for all dietary experiments. Animals were fed either a low fat, biotin-free diet consisting of 30% spray-dried egg white, 65% sucrose, salts, and vitamins excluding biotin, or a similar diet (with casein in place of egg white) that was supplemented with biotin. After 2 weeks on the deficient diet, animals weighed about 100 g, and were then used for the
homogenates were centrifuged at 105,000 x g for 45 min. The supernatant solution was then centrifuged at 105,000 x g for 10 min. The supernatant solution was then passed over a Sephadex G-25 column and eluted with 0.01 M potassium phosphate, pH 7.5, containing 0.001 M EDTA and 0.005 M 2-mercaptoethanol. The protein eluate from this column was used for subsequent experiments. Epididymal adipose tissue homogenates were centrifuged at 49,000 x g for 10 min. The supernatant solution was then centrifuged at 105,000 x g for 45 min. The resultant supernatant solution was then passed over a Sephadex G-25 column and eluted with 0.01 M potassium phosphate, pH 7.5, containing 0.001 M EDTA and 0.005 M 2-mercaptoethanol. The protein eluate from this column was used for subsequent experiments. Epididymal adipose tissue homogenates were centrifuged at 105,000 x g for 45 min, and the supernatant solutions were used for subsequent experiments.

**Enzyme Assays**—Acetyl-CoA carboxylase activity was measured as described previously (7). One unit of enzyme activity is equal to 1 pmole of malonyl-CoA formed per min at 37\°C. In those experiments in which acetyl-CoA carboxylase was titered with antibody, antiseraum was added directly to the preliminary incubation mixture as described previously (3). Antibody to acetyl-CoA carboxylase was prepared in rabbits with chicken liver acetyl-CoA carboxylase as antigen. The preparation, specificity, and activity of this antibody have been described (3).

The enzymatic conversion of apoacetyl-CoA carboxylase and biotin to holoenzyme was assayed as follows: 20 \mu moles of Tris-HCl, pH 7.5, 6 \mu moles of magnesium chloride, 7 \mu moles of potassium citrate, 1 \mu mole of 2-mercaptoethanol, 0.3 mg of bovine serum albumin, 0.24 unit of avidin, and enzyme in a volume of 0.25 ml were incubated for 5 min at 37\°C (first incubation). The addition of avidin to the first incubation mixture serves to inactivate any endogenous acetyl-CoA carboxylase contained in the extracts, thus lowering the background activity and greatly increasing the sensitivity of the subsequent holoenzyme assay. When extracts from animals fed biotin-deficient diets were used, in which endogenous enzyme levels were low, the preliminary treatment with avidin was not necessary. Excess d-biotin (0.02 mg) was then added, and the reaction mixture was incubated for an additional 5 min at 37\°C (second incubation). The synthesis of holoenzyme was initiated by the addition of 0.14 \mu mole of ATP, and the reaction mixture was incubated in a total volume of 0.26 ml for 30 min at 37\°C (third incubation). The citrate allows the newly synthesized holoenzyme to aggregate into its active polymeric form during this incubation. The holoenzyme formed in the third incubation is measured by the standard acetyl-CoA carboxylase assay by the addition of 0.05 \mu mole of acetyl-CoA, 0.7 \mu mole of ATP, and 5 \mu moles of potassium bicarbonate (1 \muCi per \mu mole), yielding a total volume of 0.23 ml. After a final incubation of 5 min at 37\°C, reactions were stopped with 0.05 ml of 10% perchloric acid, and aliquots of the reaction mixture were spotted on planchets which were dried and then counted in a gas flow counter as described previously (7).

Liver propionyl-CoA carboxylase activity was determined by the method of Halenz and Lane (8). Protein was measured by the method of Lowry et al. (9).

**Immunological Procedures**—Ouchterlony double diffusion patterns and quantitative precipitation tests were performed as outlined by Ouchterlony (10) and by Kabat and Mayer (11). Liver extracts were prepared for quantitative precipitation reactions on DEAE-cellulose as described previously (3). For direct titering experiments with antibody, crude extracts after Sephadex G-25 chromatography were found to be satisfactory. In preliminary experiments, it was shown that rat epididymal fat pad acetyl-CoA carboxylase was both inactivated and precipitated by the antibody to chicken liver acetyl-CoA carboxylase. Further, it was found that the crude 105,000 x g supernatant was satisfactory for all immunological procedures. No preliminary purification was required for precipitation reactions, as nonspecific precipitation of protein did not occur in adipose tissue extracts.

**Substrates** Acetyl-CoA was synthesized by the method of Simon and Shemin (12) with coenzyme A obtained from P-L Biochemicals. "C-Sodium bicarbonate and "H-biotin were purchased from New England Nuclear, avidin was purchased from Worthington, and d-biotin from Nutritional Biochemicals. Other substrates and cofactors were obtained from commercial sources.

### RESULTS

**Effect of Biotin on Acetyl-CoA Carboxylase Levels**—In initial studies of biotin deprivation, the standard technique using liver propionyl-CoA carboxylase levels to assess the biotin-deficient status of animals was used. In the course of these studies, it was discovered that adipose tissue acetyl-CoA carboxylase levels fell to levels 2- to 6-fold below normal within 1 to 2 weeks of biotin deprivation, during which time propionyl-CoA carboxylase levels remained near normal. Thus, after 11 days of biotin deprivation, liver propionyl-CoA carboxylase activity measured in acetone powder extracts remained normal (0.1 \mu mole of propionyl-CoA formed per hour per mg of protein). After 3 weeks of biotin deprivation, propionyl-CoA carboxylase activity fell to 0.03 \mu mole per hour per mg of protein. The effect of biotin deprivation on acetyl-CoA carboxylase levels in liver and adipose tissue is shown in Table I. Levels of acetyl-CoA carboxylase in liver decreased about 43\% with biotin deprivation, whereas adipose tissue activity fell over 3-fold in this experiment. Similarly, when biotin-deprived animals were injected with biotin 2 hours prior to death, minimal changes in liver enzyme activity were observed, while adipose tissue activity increased 7-fold over activities seen in uninjected animals. This experiment demonstrates that adipose tissue is much more sensitive to biotin deprivation than is liver, and that injection of biotin into deficient animals results in little change in liver acetyl-CoA carboxylase, whereas adipose tissue enzyme levels rise promptly to levels 2.3-fold greater than in low-fat-fed, sufficient animals. We next investigated the mechanism of these increased enzyme levels in adipose tissue.

The effect of biotin dosage on acetyl-CoA carboxylase activity in adipose tissue of biotin-deprived rats is shown in Fig. 1. Maximal response was seen with injection of 20 to 25 \mu g of d-biotin in 100-g rats, whereas a marked 4-fold response was seen with levels as low as 0.05 \mu g. If one assumes that the intrinsic specific activity of liver and adipose tissue acetyl-CoA carboxylase is the same, then of the 0.05 \mu g of biotin injected, ap-
Biotin deficiency was produced by maintaining the animals on a low fat diet for 17 days. Pair weight controls received a low fat diet for 3 days. Those animals receiving biotin supplements were injected with 100 μg of d-biotin and were killed 2 hours following injection. Liver and epididymal adipose tissue were immediately removed, and the enzyme was prepared and assayed as described under "Methods." Each determination represents data from pooled tissues of two rats.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Biotin injected</th>
<th>Acetyl-CoA carboxylase activity (milliunits/mg protein)</th>
<th>Liver</th>
<th>Adipose tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low fat diet</td>
<td>+</td>
<td>5.4, 4.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low fat, biotin-deficient diet</td>
<td>-</td>
<td>3.1, 1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low fat, biotin-deficient diet</td>
<td>+</td>
<td>5.0, 10.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Effect of biotin on adipose tissue acetyl-CoA carboxylase activity. Animals maintained on a low fat, biotin-deficient diet for 7 days were subsequently given intraperitoneal injections with increasing amounts of d-biotin. Two hours following injection, the animals were killed, the epididymal adipose tissue was removed, and the enzyme was prepared and assayed as described under "Methods." Each point represents the determination from extract pooled from two animals.

Approximately 10% was incorporated into the acetyl-CoA carboxylase of the epididymal fat pad.

This rise in enzyme activity occurred rapidly after biotin injection. Animals killed 2 min following intraperitoneal biotin injection had 12.4 milliunits per mg of acetyl-CoA carboxylase activity in adipose tissue, compared with 2.7 milliunits per mg in similarly fed, uninjected controls. The time elapsed from killing of the animals until the completion of homogenization at 0° was an additional 5 min. Since subsequent experiments have demonstrated the conversion in vitro of apocarboxylase to holoenzyme with the use of homogenates of adipose tissue, it is impossible to be certain about the speed of restoration of enzyme activity. The rapidity of restoration of enzyme activity in adipose tissue following biotin injection suggests that the prothetic group biotin is being attached to a pre-formed precursor, acetyl-CoA apocarboxylase, which has accumulated in adipose tissue during the period of biotin deprivation.

Demonstration of Acetyl-CoA Apocarboxylase in Adipose Tissue from Biotin-deficient Animals—The possibility that animals deprived of biotin while on a low fat diet accumulate acetyl-CoA apocarboxylase was investigated with antibody against acetyl-CoA carboxylase. This antibody has been previously shown to inactivate and precipitate quantitatively both aggregated and disaggregated forms of liver acetyl-CoA carboxylase (3). In preliminary experiments, it was shown that this same antibody precipitated and inactivated adipose tissue acetyl-CoA carboxylase.

Previous studies with rat liver demonstrated that there is a constant amount of immunologically precipitated enzyme per unit of enzyme activity under widely varying dietary conditions and enzyme specific activity (3). If extracts contain apoenzyme that is immunologically reactive but enzymatically inactive, the titer of extracts from biotin-deficient animals should differ from that seen in biotin-supplemented animals. The results of these titer experiments are shown in Figs. 2 and 3. Extracts of liver and adipose tissue from animals which were on a fat-free, biotin-free diet for 8 days were titered with antibody as described previously (3). If extracts contain apoenzyme that is immunologically reactive but enzymatically inactive, the titer of extracts from biotin-deficient animals should differ from that seen in biotin-supplemented animals. The results of these titer experiments are shown in Figs. 2 and 3. Extracts of liver and adipose tissue from animals which were on a fat-free, biotin-free diet for 8 days were titered with antibody as described previously (3). In one group of animals, biotin was injected 1 hour prior to killing the animals. Biotin injection had no effect on the antibody titers obtained with the use of liver extracts, as shown in Fig. 2, whereas the titer obtained with adipose tissue changed markedly (Fig. 3). These experiments are summarized in Table II. Enzyme activity did not increase significantly in liver extracts after biotin injection, and there was no change in immunological titer in these extracts (3.5 milliunits of enzyme inactivated per μl of antibody added). Similar titers were obtained with liver extracts from rats fed...
deficient after 30 days on the biotin-free diet. The difference between low fat fed and biotin-deficient animals reflects the conversion of apoenzyme to holoenzyme. The marked rise in titer and enzyme activity thus suggests that the low titer observed in adipose tissue from deficient rats is due to the accumulation in adipose tissue of large amounts of immunologically active but catalytically inactive apoenzyme. The marked rise in titer and enzyme activity thus reflects the conversion of apoenzyme to holoenzyme. The lack of a corresponding change in liver suggests that, under these conditions, apoenzyme does not accumulate in liver. The reason for the lesser change in antibody titer compared with liver suggests that, under these conditions, apoenzyme remains even in injected animals. This interpretation is supported by experiments in vitro described below, in which apoenzyme has been directly demonstrated in extracts from animals previously injected with excess biotin.

We next demonstrated that <sup>3</sup>H-biotin is incorporated directly into acetyl-CoA carboxylase in adipose tissue of deficient animals. In these experiments, rats were fed either a low fat diet or a low fat, biotin-deficient diet and were injected with <sup>3</sup>H-biotin 20 min prior to death. Acetyl-CoA carboxylase was then isolated from extracts of liver and adipose tissue by immunological precipitation. There was a low level of biotin incorporation into acetyl-CoA carboxylase from both liver and adipose tissue of low fat fed rats, as shown in Table III. This incorporation is presumed to reflect the amount of biotin incorporation associated with apoenzyme. The difference between low fat fed and biotin-deficient animals reflects the conversion of apoenzyme to holoenzyme (895 cpm per mg for adipose tissue). There was a minimal increase in incorporation of biotin into liver enzyme (65 cpm per mg); this may reflect the presence of a small amount of apoenzyme in the livers of these animals, which were severely deficient after 30 days on the biotin-free diet. The difference between liver and adipose tissue is again striking, as 8-fold more biotin was incorporated into adipose tissue compared with liver under these conditions.

Conversion in Vitro of Acetyl-CoA Apocarboxylase to Holoenzyme—The crude 105,000 × g supernatant solution derived from adipose tissue was found to catalyze the conversion of acetyl-CoA apocarboxylase to holoenzyme, as shown in Table IV. The holocarboxylase synthetase reaction took place during the third incubation (see "Methods"). The crude 105,000 × g supernatant fraction of the adipose tissue was used directly in the immunological precipitation. The 105,000 × g supernatant fraction from liver was prepared for immunological analysis as described elsewhere (3). These fractions were divided into several small aliquots, each aliquot containing at least 150 milliunits of enzyme per ml. To ensure maximal precipitation, purified carrier acetyl-CoA carboxylase was added to those fractions containing less than this amount. Antibody was added in 1.2-fold excess to each fraction to ensure complete precipitation. A corresponding amount of control rabbit serum was added to three of the aliquots in order to determine the extent of nonspecific precipitation. After the addition of 0.2 mg per ml of sodium azide, samples were incubated for 30 min at 37°, followed by incubation at 4° for 24 to 36 hours. The precipitates were collected by centrifugation and, after being washed three times in ice-cold 0.9% sodium chloride, were dissolved in formic acid and counted in a liquid scintillation counter.

### Table II

<table>
<thead>
<tr>
<th>Injection</th>
<th>Liver</th>
<th>Adipose tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enzyme activity</td>
<td>Antibody titer</td>
</tr>
<tr>
<td>NaCl solution</td>
<td>3.8</td>
<td>3.5</td>
</tr>
<tr>
<td>Biotin, 100 μg</td>
<td>4.7</td>
<td>3.5</td>
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</table>

### Table III

<table>
<thead>
<tr>
<th>Tissue</th>
<th>1. Low fat diet</th>
<th>2. Low fat, biotin-deficient diet</th>
<th>2 - 1</th>
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</thead>
<tbody>
<tr>
<td>Adipose</td>
<td>60</td>
<td>955</td>
<td>895</td>
</tr>
<tr>
<td>Liver</td>
<td>55</td>
<td>120</td>
<td>65</td>
</tr>
</tbody>
</table>
Acetyl-CoA carboxylase in biotin deficiency

Complete system. ......................

- Biotin, second incubation. .......... 0.09
- ATP, third incubation. .......... 0.15

Carboxylase assay

- ATP. .......................... 0
- Ac-CoA. ..................... 0
- Citrate.......................... 0.06

Complete system. ...................... 0.3

**FIG. 4.** Formation of acetyl-CoA holocarboxylase from extract of rat adipose tissue. Three animals on a biotin-deficient diet for 14 days were killed, and the adipose tissue was homogenized directly in 1.5 M sucrose. Following centrifugation at 105,000 × g for 45 min, the supernatant was collected and assayed for holocarboxylase synthetase activity as described under “Methods.” Avidin was included in the first incubation to reduce endogenous acetyl-CoA carboxylase activity.

inactivation of acetyl-CoA carboxylase. Thus, incubation for 1 hour resulted in some increase in holoenzyme synthesis compared with incubation for 30 min, but the increase was not linear. The effect of increasing concentration of extract on formation of acetyl-CoA carboxylase is shown in Fig. 4. The shape of this curve presumably derives from the fact that the extract contained both apoenzyme and the holoenzyme synthetase. The prior incubation of extracts to be tested with avidin reduced the blank value by inactivating any pre-formed enzyme. The holoenzyme synthetase reaction required both ATP and biotin, as shown in Table IV. The product of the holoenzyme synthetase reaction was shown to be acetyl-CoA carboxylase from the following: (a) the requirements for 14C-bicarbonate fixation step to reduce endogenous acetyl-CoA carboxylase activity.

**Table IV**

<table>
<thead>
<tr>
<th>Omissions or additions</th>
<th>Acetyl-CoA carboxylase activity (milliliters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete system. .......</td>
<td>1.47</td>
</tr>
<tr>
<td>- Biotin, second incubation</td>
<td>0.09</td>
</tr>
<tr>
<td>- ATP, third incubation</td>
<td>0.15</td>
</tr>
<tr>
<td>Carboxylase assay</td>
<td></td>
</tr>
<tr>
<td>- ATP ......</td>
<td>0</td>
</tr>
<tr>
<td>- Ac-CoA. ........</td>
<td>0</td>
</tr>
<tr>
<td>- Citrate. .............</td>
<td>0.06</td>
</tr>
<tr>
<td>Complete system. ......</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Animals were subjected to dietary alterations as indicated. Two animals were maintained on a low fat diet for 7 days, and six animals were fed a low fat, biotin-deficient diet for 20 days. The three biotin-deficient animals receiving biotin supplementation were injected with 100 μg of d-biotin 1 hour before death. Each assay tube contained 0.5 ml of protein, and holocarboxylase synthesis was assayed as described under "Methods." In these experiments, avidin was added in the first preliminary incubation step to reduce endogenous acetyl-CoA carboxylase activity.

<table>
<thead>
<tr>
<th>Dietary treatment</th>
<th>Acetyl-CoA carboxylase activity (milliliters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low fat. ..........</td>
<td>0.24</td>
</tr>
<tr>
<td>Low fat, biotin-deficient.</td>
<td>1.71</td>
</tr>
<tr>
<td>Low fat, biotin-deficient, injected with biotin.</td>
<td>1.70</td>
</tr>
</tbody>
</table>

were those of acetyl-CoA carboxylase; (b) the activity was destroyed by specific antibody to acetyl-CoA carboxylase; and (c) the product of the CO₂ fixation reaction was isolated and shown to be malonyl-CoA, as described previously (13).

The ability of extracts from adipose tissue of rats fed various diets to synthesize acetyl-CoA holocarboxylase was next investigated. Extracts from low fat-fed rats showed minimal acetyl-CoA holocarboxylase formation, as shown in Table V, whereas extracts from either biotin-deficient or biotin-injected animals catalyzed the formation of acetyl-CoA carboxylase. The formation of holoenzyme in vitro, with the use of extracts from animals previously injected with excess biotin, suggests that some apoenzyme remained in these extracts. The reason for equal holoenzyme formation with either injected or uninjected extracts is unexplained. Either the conditions of assay are not optimal for complete conversion of apoenzyme to holoenzyme, or the holoenzyme formed inhibits further conversion of apoenzyme in both extracts. It is also possible that the holoenzyme synthetase is rate-limiting in both extracts. In the course of these experiments, it was found that the acetyl-CoA carboxylase-synthesizing activity was unstable when stored at 4° in the usual buffer. When adipose tissue was homogenized directly in 1.5 M sucrose (1.5 ml of sucrose per g of tissue), the activity was stable for several weeks at 4°. Preliminary characterization of this activity indicated that it was destroyed by boiling, and no activity was contained in any of the particulate fractions from adipose tissue. When 105,000 × g supernatant from liver was used in this assay, no acetyl-CoA carboxylase-synthesizing activity was seen, presumably because of a lack of apoenzyme.

**Discussion**

We have confirmed the fact that adipose tissue acetyl-CoA carboxylase is markedly sensitive to biotin deprivation. In addition, we have demonstrated that apoenzyme accumulates when enzyme activity decreases in adipose tissue following biotin deprivation. The evidence for accumulation of apoenzyme in this tissue is 4-fold: (a) the rapid rise in enzyme activity following biotin injection into deficient animals; (b) the low antibody titer in deficient animals, which increases following biotin injection; (c) the incorporation of 3H-biotin into acetyl-CoA carboxylase following the injection of 3H-biotin in deficient...
animals; (d) the formation in vitro of acetyl-CoA holocarboxylase by deficient adipose tissue extracts incubated with d-biotin and ATP. These phenomena were demonstrated as soon as 4 days after initiating a biotin-free diet, during which time liver acetyl-CoA carboxylase levels remained normal. In liver, propionyl-CoA carboxylase levels fell 4-fold by 3 weeks of biotin deprivation, while acetyl-CoA carboxylase fell by only 50%, even in severely deficient animals, after prolonged biotin deprivation. The mechanism of this marked difference in response of liver and adipose tissue to biotin deprivation remains unexplained. The marked sensitivity of adipose tissue is not due to an inability of the tissue to compete with other organs for biotin uptake. When a limiting dose of 0.05 pg of biotin was injected into de-

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