Metabolism of Glycine by Avian Liver

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The carboxyl carbon of glycine is converted to CO₂ approximately 5 times as rapidly as the α-carbon by normal rat liver homogenates (1, 2). This difference is due to the versatility of the α-carbon as a source for one carbon units in synthetic processes. An impairment in the conversion of both carbon atoms to CO₂ was demonstrated in livers from rats fed purified diets unsupplemented with folic acid or vitamin B₁₂ (2).

Subsequent comparative studies showed a considerably more active system in pigeon liver homogenates for the production of CO₂ from the carboxyl carbon, whereas essentially no CO₂ was formed from the α-carbon; most of the α-carbon appeared in glycine. Totter et al. (3) found that livers from folic acid-fed rats produced significantly more CO₂ from the carboxyl carbon than from the α-carbon. Vohra et al. (4) found that in pigeon liver homogenates, CO₂ formation was impaired in folic acid, vitamin B₁₂, and niacin deficiencies, and the activity was restored by the addition of the corresponding cofactors, viz. tetrahydrofolate, pyridoxal phosphate, and diphosphopyridine nucleotide. A simultaneous appearance of CO₂ and serine (from the C-1 fragment and unreacted glycine) was observed. Glyoxylate did not appear to be an intermediate in the formation of CO₂.

EXPERIMENTAL PROCEDURE

CO₂ Formation—The birds were decapitated, the livers were removed and immediately chilled in ice, and a 10% homogenate was prepared with cold 0.15 M KCl. The homogenate was centrifuged at 0°C for 10 minutes at 600 × g. The precipitate was resuspended in the KCl solution and centrifuged again. This "washed" precipitate was resuspended in KC1 and diluted to the volume of the original homogenate. This is called the "particulate fraction" in the text. Sanadi and Bennett (5) reported that serine is synthesized from glycine in mitochondrial preparations obtained from chicken livers by differential centrifugation in 0.3 M sucrose. We observed a close relationship between CO₂ production from the carboxyl carbon and serine synthesis in the particulate fraction or in mitochondria prepared in sucrose. Since the particulate fraction was at least as active as the mitochondrial preparation, and since sucrose interfered with the colorimetric determination of serine, this preparation was used in these studies.

Whole homogenate or the particulate fraction equivalent to 80 mg of fresh liver was incubated with 30 μmoles of glycine-1-C₁⁴ (3000 c.p.m. per μmole) for 1 hour in air. Details of the incubation procedure, the collection of CO₂ and the measurement of radioactivity have been described previously (2). The following modifications were made: (a) cytochrome c was omitted from the incubation medium, and (b) BaCO₃ was prepared from one-sixth of the sodium carbonate solution and was counted on filter paper. Correction to infinite thinness under these conditions of counting was made by multiplying the counts by 2.5. This factor was determined experimentally. The glycine-1-C₁⁴ was oxidized with Van Slyke-Folch reagent in a Barker apparatus as described by Calvin et al. (6); the CO₂ was collected in NaOH and counted by the identical procedure used above.

Serine—Once it was established by ion exchange chromatography (7) that the major portion of the nonglycine radioactivity in the incubated mixture resided in the serine fraction, trichloroacetic acid filtrates of the mixtures were analyzed for total serine, rather than for serine-C₁⁴, by the periodate-chromotropic acid method as described by Friesel and Mackenzie (8).

Ammonia—The vessel contents were deproteinized with tungstic acid. The ammonia was distilled in a Jenden-Taylor Kjeldahl distillation apparatus (9) into 0.1 N HCl and determined with Nessler's reagent.

Glycine and Glyoxylate—Colorimetric methods for the determination of glycine and glyoxylate were based on the procedures described by Christensen et al. (10) and by Pesce and Ferrero (11), respectively.

Vitamin-deficient Diets—Appropriate vitamins were omitted from the casein-gelatin diet used previously (12). The diets were fed to day-old Peking ducklings. Drackett C-1 soy protein, supplemented with 0.75% methionine and 0.4% glycine, was substituted for the casein and gelatin in the vitamin B₁₂-deficient diet. The ducks were used when they were 8 to 15 days old. Control ducks received the purified diets supplemented with the appropriate vitamins. In all experiments with pigeon and chicken livers, the birds were fed commercial chicken feed.

Liver Extract—The preparation referred to as liver extract in the text was prepared by heating a 10% liver homogenate in...
1.1% KCl solution in a boiling water bath for 10 minutes and removing the coagulated protein by centrifugation.

RESULTS

In several preliminary experiments with pigeon liver homogenates, it was found that incubation of 10 μmoles of glycine (labeled in either the α or the carboxyl position) for 2 hours with 200 mg of liver produced about 4 μmoles of CO₂ from the carboxyl carbon and 0.02 μmole from the α-carbon. Approximately 79% of the glycine was converted to serine (calculated on the basis that 2 molecules of glycine are required to form 1 molecule of serine), 14% to hypoxanthine, 7% remained unchanged, and 7% was undetermined. Totter et al. (3) found that 8.7% of glycine-1-C¹⁴ incubated with chicken liver was found in guanidinoacetic acid, 36.4% in serine, and small amounts in purines and pyrimidines.

Nutritional Deficiency Studies—The formation of C⁴O₂ from glycine-1-C¹⁴ was decreased in the homogenates of livers from ducks deficient in vitamin B₆, niacin, and folate acid (Table I). Omission of vitamin B₁₂ from the diet had no effect. It was

<table>
<thead>
<tr>
<th>Table I</th>
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<tbody>
<tr>
<td><strong>Glycine Metabolism</strong></td>
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<td><strong>Vol. 237, No. 1</strong></td>
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</tbody>
</table>

### Assumed that the ducks were at least partially deficient in vitamin B₁₂ on the basis of body weights at 15 days of age; the deficient and control groups averaged 417 and 551 g, respectively. Hemoglobin concentrations were 10.5% and 11.4%, respectively. Serine values are included in the table to illustrate the simultaneous effects of the deficiencies on the release of carboxyl carbon as CO₂ and the formation of serine.

Addition of pyridoxal-5-P, DPN, or 5-formylfolate-H₄ to the appropriate liver homogenates prepared from vitamin-deficient birds restored both activities toward the control levels. Hence, the results with pyridoxal-5-P and DPN corroborate the stimulatory effects of these cofactors in the particulate fraction of normal liver (see below).

The folate acid deficiency studies were pertinent in that the influence of folate-H₄ could not be observed in control liver homogenates or even in the particulate fractions.

The concentration (0.045 μmole) of 5-formylfolate-H₄, which was stimulatory in the deficient whole homogenate was not effective in the particulate fraction (Table II), perhaps because of a loss of the system that converts it to the active cofactor (13). However, 1 μmole of folate-H₄ approximately doubled the amount of CO₂ produced in both the homogenate and the particulate fraction. Serine synthesis was stimulated to the same extent (tested in the particulate fraction).

**Activity In Homogenate versus Particulate Fraction of Normal Liver**—The particulate fractions were from 30 to 50% as active as the original homogenates (Table III). The activities in pigeon and duck liver preparations were restored to between 76 and 84% of the homogenates by corresponding liver extracts. Chicken liver extracts were slightly inhibitory.

It can also be observed in Tables III and IV that DPN and pyridoxal-5-P alone or together stimulated the activity of the particulate fractions. Usually, the two cofactors together were somewhat more effective than either alone, but did not restore the activities to the same extent as the liver extracts. Lipoid acid, thiamine pyrophosphate, FAD, coenzyme A, or ATP did not enhance the effectiveness of DPN.

Incubation of the particulate fraction at 37° before the addition of glycine substrate inactivated the system. Liver extract pro-

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* In vitamin B₆ deficiency, pyridoxal-5-P, 0.2 mg; in niacin deficiency, DPN-4H₂O, 1 mg; in folate acid deficiency, 5-formylfolate-H₄, 0.02 mg per vessel. Each vessel also contained fresh liver, 80 mg, glycine-1-C¹⁴, 30 μmoles (3000 c.p.m./μmole), MgCl₂, 10.9 μmoles, KCl, 330 μmoles, potassium phosphate, pH 7.4, 33 μmoles, and water in a total volume of 3 ml.

† Standard error of the mean. The differences in CO₂ and serine between the control and deficient livers were significant at levels of p = 0.01 or less.

‡ 5-Formylfolate-H₄ was not tested in these particular control birds. However, it did not stimulate the formation of either CO₂ or serine when tested in a number of other control experiments.

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CO₂ formation from glycine carboxyl carbon in normal pigeon, duck, and chicken liver homogenates and in particulate fractions

<table>
<thead>
<tr>
<th>Species</th>
<th>No.</th>
<th>+ Liver extract</th>
<th>+ DPN</th>
<th>+ Pyridoxal-5-P</th>
<th>+ Folate-H₄</th>
<th>+ DPN + Folate-H₄</th>
</tr>
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<tr>
<td>Pigeon</td>
<td>9</td>
<td>29.8</td>
<td>8.9</td>
<td>24.0</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>48.0</td>
<td>23.2</td>
<td>25.4</td>
<td></td>
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<tr>
<td>Duck</td>
<td>9</td>
<td>48.0</td>
<td>22.1</td>
<td>40.2</td>
<td>31.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>40.4</td>
<td>15.3</td>
<td>28.0</td>
<td>21.6</td>
<td>23.5</td>
</tr>
<tr>
<td>Chicken</td>
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<td>65.2</td>
<td>31.0</td>
<td>34.2</td>
<td>26.2</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>59.3</td>
<td>29.5</td>
<td>32.6</td>
<td>22.6</td>
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</tbody>
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* Each vessel contained the particulate fraction equivalent to fresh liver, 80 mg, normal liver extract, 0.8 ml, glycine-1-C¹⁴, 30 μmoles, MgCl₂, 30.9 μmoles, KCl, 330 μmoles, potassium phosphate, pH 7.4, 33 μmoles, and water in a total volume of 3 ml.
† DPN-4H₂O, 1 mg, and pyridoxal-5-P, 0.2 mg per vessel.

**Effects of pyridoxal-5-P, DPN, and folate-H₄ on formation of CO₂, NH₃, and serine by particulate fraction of normal pigeon liver**

<table>
<thead>
<tr>
<th>Addition*</th>
<th>CO₂, μmoles/g liver/hr</th>
<th>NH₃, μmoles/g liver/hr</th>
<th>Serine, μmoles/g liver/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>9.6</td>
<td>6.5</td>
<td>8.0</td>
</tr>
<tr>
<td>Pyridoxal-5-P</td>
<td>15.3</td>
<td>11.0</td>
<td>12.5</td>
</tr>
<tr>
<td>DPN</td>
<td>13.5</td>
<td>13.9</td>
<td>12.1</td>
</tr>
<tr>
<td>Folate-H₄</td>
<td>9.3</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Pyridoxal-5-P + DPN</td>
<td>20.1</td>
<td>19.5</td>
<td>15.8</td>
</tr>
<tr>
<td>DPN + Folate-H₄</td>
<td>19.5</td>
<td>17.9</td>
<td>14.5</td>
</tr>
</tbody>
</table>

* DPN-4H₂O, 1 mg, pyridoxal-5-P, 0.2 mg, or folate-H₄, 0.3 mg per vessel.
† Average values from four different pigeon livers.

**Studies with Glyoxylate**—On the basis of the following evidence, free glyoxylate did not seem to be an intermediate in the formation of CO₂ from the glycine carboxyl group in avian liver as was proposed for rat liver by Nakada et al. (14).

1. Very little CO₂ was produced from glyoxylate under conditions of reduced O₂ tension was measured to see whether the release of CO₂ and of NH₃ were both dependent on oxygen. After the vessels were loaded and chilled, they were flushed with commercial nitrogen without attempting to replace the O₂ completely. In one set of experiments, there was a release of approximately half as much CO₂ and NH₃ (48 and 52%, respectively) as in air, and in another the values were 23 and 27%, respectively. This suggested that the release of each component was equally dependent on oxygen.

**The Effect of Reduced O₂ Tension**

- CO₂ and NH₃ release of CO₂ and NH₃ and the synthesis of serine can be observed in Tables IV and V. Conditions which decreased CO₂ production also decreased the release of NH₃ and the synthesis of serine, and factors which stimulated one also stimulated the others.

**Inhibition Studies**—Of the pyridoxal-5-P antagonists studied, isonicotinylhydrazide, but not penicillamine or deoxypyridoxine, was inhibitory to CO₂ production (Table VI). The inhibition was reversed by pyridoxal-5-P. 4-Aminopteroylglutamate was without effect. Formaldehyde, but not acetaldehyde, was inhibitory.

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The work of Nakada et al. (14) has indicated that the principal degradative pathway for glycine proceeds via glyoxylic acid in rat liver. The evidence presented against the formation of free glyoxylate in bird liver makes it unlikely that glyoxylate is an intermediate in this species. The close relationship between the liberation of CO₂ and NH₃ and the synthesis of serine, and the influence of DPN, pyridoxal-5-P, and tetrahydrofolate on all of these, particularly including the release of carboxyl carbon as CO₂ are consistent with the pathway described for D. glycino-philus by Sagers and Gunsalus (15). Extracts of this microorganism utilized glycine as an electron donor via DPN, and this was accompanied by liberation of CO₂ from the glycine carboxyl group and transfer of the α-carbon of glycine to folate-H₄. The system was dependent on pyridoxal-5-P.

On the assumption that the sensitivity of the release of the carboxyl CO₂ to variations in the levels of pyridoxal-5-P, DPN, and folate-H₄ in the avian liver preparations is indicative of direct participation of these cofactors in the reaction, then pyridoxal-5-P would seem to have a dual role in the synthesis of serine from glycine, one in the decarboxylation of glycine and one in the synthesis of serine from CH₃OH-folate-H₄ and glycine (18).

Sagers and Gunsalus found the reaction for the decarboxylation of glycine to be as follows:

H₄CNH₂COOH + folate-H₄ → DPN, H₂O + pyridoxal-5-P

CH₃OH-folate-H₄ + CO₂ + NH₃ + 2H

The balanced reaction for the synthesis of serine from glycine also involves the liberation of 2 electrons:

2H₄CNH₂COOH + H₂O → CO₂ + NH₃ + HOCH₂CHNHzCOOH + 2H

The precise mechanisms by which the three cofactors could participate in the decarboxylation of glycine have not yet been defined. The following hypothetical formulations would explain the derivation of electrons from glycine, and coordinate the three different cofactors in the decarboxylation reaction. The formulations involve a hydride transfer reaction (19) between the α-carbon of glycine (perhaps from a Schiff's base complex with pyridoxal-5-P) and DPN. The possibility of the direct hydrogen transfer to DPN in the oxidation of substrates, such as ethanol and lactic acid (20), occurring as a one-step transfer of a hydride ion, has been discussed by Westheimer (21) and others. The hydride transfer from glycine to DPN would leave a positively charged carbonium ion, which could be attracted to the electron pairs of the N⁺ (or N₂⁺) nitrogen of tetrahydrofolate. Subsequent loss of CO₂ and reaction of the complex with water could regenerate pyridoxal-5-P with the liberation of ammonia and 5-10-methylene(tetrahydrol)folate. These hypothetical formulations are illustrated in Scheme 1.

**SUMMARY**

An homogenate from pigeon, duck, or chicken liver released from 30 to 70 μmoles of CO₂ per g of fresh liver per hour from the carboxyl group of glycine without forming more than a trace...
of CO$_2$ from the $\alpha$-carbon; most of the $\alpha$-carbon reacted with another molecule of glycine to form serine.

A KCl-washed particulate fraction of liver was from 30 to 50% as active as whole homogenate. A boiled liver extract restored the activities to about 80% of that in the homogenate (except in chicken liver in which the extract was inhibitory). Part of the stimulatory effect of the extract could be accounted for by DPN and pyridoxal 5-phosphate.

The rate at which glycine was decarboxylated was decreased in homogenates of livers from vitamin B$_6$-, niacin-, and folic acid-deficient ducks. Each corresponding cofactor, pyridoxal 5-phosphate, DPN, and tetrahydrofolic acid, was stimulatory when added to the corresponding deficient homogenate.

A close relationship in the production of CO$_2$ and NH$_3$ and the synthesis of serine existed in that factors which affected one of these also affected the others to essentially the same extent.

Free glyoxylate did not seem to be an intermediate in the process by which glycine was metabolized in avian liver.

REFERENCES

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