The Tracing of the Pathway of Mevalonate's Metabolism to Other Than Sterols*

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Specifically 14C-labeled mevalonate acids were administered to rats in diabetic ketosis, and the distribution of 14C was determined in the hydroxybutyric acid each rat excreted. Also, the distributions of 14C were determined in hydroxybutyric acid formed by slices of livers and kidneys from rats in diabetic ketosis and incubated with the specifically labeled mevalonate acids. The distributions found are in accord with the conversion of mevalonate to hydroxymethylglutaryl-CoA by the shunt pathway proposed by J. Edmond and G. Popják (1977) J. Biol. Chem. 249, 66-71. That is, carbon 5 of mevalonate was metabolized to form the carboxyl of acetyl-CoA and carbons 2 and 3 of mevalonate were converted in large measure to hydroxybutyric acid without acetyl-CoA as an intermediate, i.e. the bond between carbon 2 and 3 was not cleaved, while the bond between 1 and 2, traced with [1,2-14C]mevalonate, was cleaved. Similar distributions of 14C were found in hydroxybutyric acid excreted by rats in diabetic ketosis administered specifically 14C-labeled isovaleric acids, isovaleric acid having in its metabolism intermediates common to those in the shunt pathway.

Edmond and Popják (1) reported that in 9-day-old rats 14C from [2-14C]mevalonate was rapidly incorporated into fatty acids. They (1, 2) postulated that this incorporation occurred through a "shunt" pathway (Fig. 1). The basis for their postulate was the demonstration that in liver isopentenyl pyrophosphate, formed from mevalonate and the precursor of sterols, can also be dephosphorylated to form dimethylallyl alcohol. This alcohol was shown to be converted to dimethylacrylic acid by a soluble protein fraction of a liver homogenate (3). Further reactions in the postulated shunt were the fixation of CO2 by the CoA derivative of the acid to form trans-3-methylglutaconyl-CoA and the latter's conversion to HMG-CoA (1, 2, 4), reactions known to occur in the hepatic metabolism of leucine via isovaleric acid (5). While Edmond and Popják (1) favored this pathway as the explanation for the incorporation of 14C into fatty acids, they considered two alternate pathways as possibilities (Fig. 1): (a) conversion of mevalonate directly to trans-3-methylglutaconyl-CoA by dehydrogenations, dehydration, and activation with CoASH, and (b) reversal of the HMG-CoA reductase-catalyzed reaction.

Estimations of the portions of mevalonate metabolized by the nonsterol- and sterol-forming pathways have been made from yields of 14CO2 and incorporations of 14C into sterols from [2-14C]mevalonate or [5-14C]mevalonate (6). With the assumption that the shunt pathway is the nonsterol-forming pathway active in kidney and using the yields of 14CO2 from the 14C-labeled mevalonates as the measure of that pathway, the kidney has been concluded to metabolize mevalonate by the pathway to a much greater extent than do other tissues (6-9).

The purpose of the present study was to determine whether the metabolism of mevalonate in kidney as well as liver is consistent with its conversion to HMG-CoA and, if so, then to determine to what extent in mevalonate's conversion to HMG-CoA its carboxyl carbon is retained, since carbon 1 of mevalonate is cleaved in the shunt pathway, but not in the alternate pathways considered by Edmond and Popják (1).

EXPERIMENTAL PROCEDURES

Materials—Female rats of the Sprague-Dawley strain, weighing 200-300 g, were used. They were fed ad libitum. Diabetes was induced in them by intravenous injection of streptozotocin after they had been fasted for 24 h, and then they were maintained with insulin for 9 to 11 days (10). Those used were the ones that developed marked ketosis along with glucosuria after the insulin was discontinued. At killing, the concentrations of glucose (11) and β-hydroxybutyrate (12) in their blood were determined. Glucose averaged 25.4 mM and hydroxybutyrate 3.4 mM.

R,S-[4-14C]Mevalonolactone (16 μCi/μmol) was purchased from the Amersham Corp., and sodium R,S-[5-14C]mevalonate (15 μCi/μmol) was from Research Products International Corp., Mount Prospect, IL. R,S-[2-14C]Mevalonolactone (17 μCi/μmol) and R-[3-14C]mevalonolactone (52 μCi/μmol) were purchased from New England Nuclear. In addition to the evidence for their purity provided by their manufacturers, the lactones were subjected to thin layer chromatography on silica gel plates using an absolute ethanol:toluene (1:4 by volume) solvent system. Each gave a single spot containing more than 99% of the 14C applied to its plate (13, 14). Oxidation of a sample of the sodium [3-14C]mevalonate by the Kuhn-Roth procedure (10) gave acetic acid with 14C localized to its carboxyl carbon while oxidation of a sample of the sodium [2-14C]mevalonate gave acetic acid devoid of 14C. The carboxyl carbon of the acetic acid should be derived from carbon 3 and the methyl carbon from carbon 6 of mevalonate.

The 14C-labeled lactones were hydrolyzed with NaOH to the sodium salts of their acids (15) just before use. There is ample evidence that the R isomer, but not the S isomer, of mevalonolactone has been reported to be better utilized by liver than its acid (17), although apparently in vivo mevalonolactone is quickly hydrolyzed (15, 18).

D,L-[2-14C]Valine (16 μCi/μmol) and D,L-[4-14C]valine (39 μCi/μmol) were also purchased from Research Products International Corp. They were deaminated (19), and the resulting [2-14C]isovaleric and [4-14C]isovaleric acids were purified by partition chromatography using a Celite (Johns-Manville No. 535) column and mixtures of chloroform and butanol equilibrated with 2 M potassium phosphate...
buffer of pH 7.6 (20). These acids gave single spots with the mobility of isovaleric acid when chromatographed on silica gel plates using a chloroform:butanol (92:5:7.5, by volume) solvent system.

**In Vivo Experiments**—The labeled compounds were injected intraperitoneally into the rats in diabetic ketosis. Urine collection was begun following the injection in 0.2 ml of 0.154 M NaCl, at the specific activity provided by the manufacturer, of one of the mevalonates (5 μCi), a mixture of [1-14C]mevalonate and [2-14C]mevalonate (5 μCi of each), or one of the isovaleric acids (5 μCi). A repeat injection was made 18 h later, and the collection of urine was terminated 18 h after that. The urines from each rat were acidified and extracted continuously with ether. Each ether extract was neutralized with NaOH and evaporated to dryness.

The resulting crude sodium hydroxybutyrate was also purified by partition chromatography (21, 22). It was acidified with H2SO4, and mixed with a small amount of Celite 535, and this mixture was transferred to the top of a column of Celite prepared for pouring a slurry of the Celite in chloroform. The column was then developed through successive additions of chloroform, chloroform plus 5% and plus 10% (by volume) of 1-butanol equilibrated with 2 N H2SO4. Mevalonic acid and/or its lactone, extracted by ether from the acidified urines, eluted in fractions of the 100% chloroform. Hydroxybutyric acid, if present in the acidified urine, would have been extracted by ether and eluted in the fractions containing hydroxybutyrate (24). But as shown by a tracing with 14C-labeled lactate, crotonic acid was purified by elution and catalytically reduced to hydroxybutyrate (25). The hydroxybutylate was added, and the hydroxybutyrate was isolated and degraded as described for incubation of slices.

**RESULTS**

Distributions of 14C in the hydroxybutyric acids excreted by the ketotic diabetic rats injected with the 14C-labeled mevalonic and isovaleric acids are recorded in Table I. When the mevalonic acid was equally labeled in its carbons 1 and 2, the hydroxybutyric acid excreted had on the average, relative to carbon 2, 0.56 times as much 14C in carbon 1 and 0.31 times as much in carbon 3, with somewhat more than twice as much 14C in carbon 2 as in its carbon 4. When the mevalonate was labeled only in carbon 2, the distribution was similar to that when its carbon 1 and carbon 2 were equally labeled, except that there was relatively less incorporation into carbons 1 and 3 of hydroxybutyric acid, although still on the average 0.29 and 0.22 times as much as in its carbon 2. With [3-14C]mevalonate as substrate, 14C was localized to carbons 1 and 3 of hydroxy-
butyric acid, with one-fifth as much 14C in carbon 1 as carbon 3. In the hydroxybutyric acid formed from [5-14C]mevalonate, 14C was also localized to carbons 1 and 3, but there was 1.1 to 1.4 times as much 14C in carbon 1 as carbon 3. [2-14C]isovaleric acid and [4-14C]isovaleric acid gave hydroxybutyric acid with 14C solely in carbons 2 and 4 with 1.3 to 1.7 times as much 14C in carbon 2 as carbon 4.

Distributions of 14C in hydroxybutyric acids formed when [2-14C]mevalonate and [1,2-14C]mevalonate were incubated with liver and kidney slices and when [1,2-14C]mevalonate was perfused through a liver from rats in diabetic ketosis are recorded in Table II. The distributions in the hydroxybutyric acid formed from [1,2-14C]mevalonate and [2-14C]mevalonate by the liver slices and the perfused liver were similar to those in the hydroxybutyric acid excreted by the ketotic rats (Table I). While there was still more than twice as much 14C in carbon 2 as carbon 4, there was much less 14C in carbons 1 and 3 of hydroxybutyric acid formed by kidney slices than in hydroxybutyric acid formed by liver preparations.

**TABLE II**

Distributions of 14C in hydroxybutyric acid formed from [2-14C] mevalonic acid and [1,2-14C]mevalonic acid by slices of livers and kidneys and a perfused liver from ketotic diabetic rats

| Labeled mevalonic acid | 14C in hydroxybutyric acid* | Recovery |
|------------------------|-----------------------------|----------|
|                        | C-1 | C-2 | C-3 | C-4 |       |
| Liver slices           |     |     |     |     |       |
| 2-14C                  | 0.22| 1.0 | 0.14| 0.33| 103   |
| 2-14C                  | 0.08| 1.0 | 0.07| 0.31| 101   |
| 2-14C                  | 0.15| 1.0 | 0.08| 0.43| 96    |
| 2-14C                  | 0.24| 1.0 | 0.01| 0.26| 100   |
| Average                | 0.22| 1.0 | 0.08| 0.33|       |
| 1,2-14C                | 1.11| 1.0 | 0.34| 0.53| 100   |
| 1,2-14C                | 0.58| 1.0 | 0.06| 0.23| 102   |
| 1,2-14C                | 0.47| 1.0 | 0.13| 0.35| 87    |
| 1,2-14C                | 0.90| 1.0 | 0.17| 0.36| 99    |
| 1,2-14C                | 0.74| 1.0 | 0.30| 0.36| 94    |
| 1,2-14C                | 0.50| 1.0 | 0.11| 0.25| 99    |
| Average                | 0.72| 1.0 | 0.19| 0.35|       |
| Kidney slices          |     |     |     |     |       |
| 2-14C                  | 0.00| 1.0 | 0.00| 0.35| 94    |
| 2-14C                  | 0.00| 1.0 | 0.00| 0.22| 100   |
| 2-14C                  | 0.02| 1.0 | 0.00| 0.53| 97    |
| Average                | 0.01| 1.0 | 0.00| 0.37|       |
| 1,2-14C                | 0.14| 1.0 | 0.01| 0.27| 92    |
| 1,2-14C                | 0.45| 1.0 | 0.06| 0.44| 98    |
| 1,2-14C                | 0.08| 1.0 | 0.01| 0.34| 108   |
| 1,2-14C                | 0.13| 1.0 | 0.03| 0.43| 100   |
| Average                | 0.20| 1.0 | 0.03| 0.37|       |
| Liver perfusion        |     |     |     |     |       |
| 1,2-14C                | 0.39| 1.0 | 0.37| 0.26| 94    |

* Values expressed relative to the 14C in carbon 1 which is set to 1.0.

**DISCUSSION**

HMG-CoA is an intermediate in all three of the postulated nonsterol-forming pathways (Fig. 1) considered possible explanations for the formation of CO2 and fatty acids from carbons 2 and 5 of mevalonic acid (1) and their incorporation into hydroxybutyric acid (30). Cleavage of the incorporation of 14C into carbons 1 and 3 of hydroxybutyric acid by the liver pathway would yield acetoacetic acid and hence hydroxybutyric acid, containing carbons 2, 3, and 6 of the mevalonic acid, and acetyl-CoA, containing carbons 4 and 5. Two molecules of acetyl-CoA can condense to form 1 molecule of acetoacetyl-CoA which can also yield hydroxybutyric acid.

Therefore, via HMG-CoA [5-14C]mevalonate should yield [1,3-14C]hydroxybutyric acid, while [2-14C]mevalonate and [3-14C]mevalonic acid should yield [2-14C]hydroxybutyric acid and [3-14C]hydroxybutyric acid. [5,14C]Mevalonic acid did yield [1,3-14C]hydroxybutyric acid (Table I). The ratio of incorporation of 14C from [5-14C]mevalonate into carbon 1 to carbon 3 of hydroxybutyric acid, 1.1 to 1.4, was the same as in hydroxybutyric acid excreted by ketotic diabetic rats injected with [1-14C]acetic acid and [1-14C]fatty acids which must have [1-14C]acetyl-CoA as an intermediate in their metabolism (29). Greater activity in carbon 1 than carbon 3 can be attributed to the formation of HMG-CoA by the condensation of labeled acetyl-CoA with unlabeled acetoacetyl-CoA formed from the terminal four carbons of fatty acids and/or formed from ketogenic amino acids, e.g. phenylalanine and leucine (29).

More than 1.1 to 1.4 as much 14C in carbon 2 as carbon 4 of hydroxybutyric acid when [2-14C] mevalonic acid was injected (1.0/0.47 = 2.1 from Table I) and in carbon 3 as carbon 1 when [3-14C]mevalonic acid was injected (1.0/0.20 = 5.0 from Table I), therefore, indicates that a significant portion of acetoacetic acid formed from mevalonate was formed without acetyl-CoA as an intermediate. This is in keeping with the formation of the acetoacetic acid from the mevalonate via HMG-CoA without cleavage of the bond between carbons 2 and 3. That there is activity in carbon 4 when [2-14C]mevalonic acid and in carbon 1 when [3-14C]mevalonic acid were administered is in accord with some of the acetoacetic acid formed from HMG-CoA being converted to acetoacetyl-CoA (31), with the acetoacetyl-CoA then being cleaved to acetyl-CoA, and the acetyl-CoA then reconverted to acetoacetic acid.

Via reversal of the HMG-CoA reductase-catalyzed reaction or the conversion of mevalonate directly to 3-methyl-3-butenyl-tacetyl-CoA (see Fig. 1) carbon 1 of mevalonate would be retained in the formation of HMG-CoA. Therefore, [1,2-14C] mevalonic acid would yield [1,2-14C]hydroxybutyric acid. Via the shunt pathway, carbon 1 is lost as CO2, so [2-14C]hydroxybutyric acid would be formed. Therefore, the formation of [2-14C]hydroxybutyric acid from [1,2-14C]mevalonic acid by kidney slices (Table II) is in keeping with the reactions of the shunt pathway and eliminates the other pathways as contributing significantly to mevalonate's metabolism in kidney.

That the distributions of 14C in hydroxybutyric acid excreted by the rats given [1,2-14C]mevalonate were similar to those in hydroxybutyric acid formed by liver slices and the perfused liver (Tables I and II) indicates that the hydroxybutyric acid that was excreted was formed primarily in the liver.

The principal organ of ketone body formation in the rat. Hydroxybutyric acid formed from [1,2-14C]mevalonic acid contained 14C in carbon 1 but so did the hydroxybutyric acid formed from [2-14C]mevalonic acid, although to a lesser extent.

Since the specific activities of carbons 1 and 2 of the [1,2-14C] mevalonic acid were the same and since the ratio of incorporation into carbon 1 to carbon 2 of hydroxybutyrate from [2-14C]mevalonate was 0.29/1.00 (Table I), if carbon 1 of mevalonate had been completely retained in the formation of HMG-CoA, as an approximation, a ratio of 1.29 would have been expected from [1,2-14C]mevalonic acid. That it was only 0.56 means that (1.29 - 0.56)/1.29 = 56% of carbon 1 was lost in the formation of hydroxybutyric acid from mevalonate. This is a minimum value in consideration of the possible explanations for the incorporation of 14C into carbons 2 and 3 of hydroxybutyric acid when [2-14C]mevalonic acid was administered.

One such explanation would be randomization in the Krebs cycle, i.e. [2-14C]acetyl-CoA --- [2,3-14C]succinic acid --- [2,3-14C]phosphoenolpyruvate --- [1,2-14C]acetyl-CoA. In the ketotic diabetic rats, conversion of pyruvate to acetyl-CoA would be expected to be minimal. This is evidenced by the
fact that when [2-14C]palmitate, which must yield [2-14C]aceto-
ethyl-CoA in its metabolism, is administered to ketotic diabetic rats,
the isotope is negligible [14C] in carbons 1 and 3 of the hydroxy-
butyrate the rats excrete (29).

Another and more likely explanation is 14CO2 fixation. There
are minor pathways by which CO2 can be fixed to become car-
bon 1 of acetate and these could become prominent, when the
conversion of the carbons of mevalonate to hydroxybutyric acid
via HMG-CoA is relatively small. Indeed, only a relatively small
amount of mevalonate is metabolized via the shunt in liver (6) and
in accord with this, the amounts of 14C incorporated into hydroxybutyric acid in this study were relatively small. The small
yields of 14C in hydroxybutyric acid may be a function of the
compartment in which HMG-CoA is formed from the mevalonate, as well as the small contribution of the shunt pathway to mevalonate’s metabolism. Formation of
HMG-CoA occurs both in mitochondria and cytoplasm (32), but formation of 3-methylglutaryl-CoA has been demonstrated
only in mitochondria (33), the location of 3-methylgluta-
aryl-CoA hydratase has not been defined (34), and HMG-
CoA lyase is present primarily in mitochondria (35).

Since 14CO2 is formed from every molecule of [1-14C]meva-
lonate metabolized by the shunt or sterol-forming pathway,
the quantity of 14CO2 formed from [2-14C]mevalonate in its
metabolism must be less than from [1-14C]mevalonate. Therefore,
assuming that 14CO2 fixation is primarily responsible for the
incorporation of 14C from [2-14C]mevalonate into carbon 1 of a hydroxybutyric acid, the quantity of 14C fixed must then
be greater for the same quantity of [1,5-14C]mevalonate as [2-
14C]mevalonate metabolized. This is the reason the estimate
that 73% of the mevalonate metabolized via HMG-CoA pro-
ceeded with cleavage of the bond between carbon 1 and 2 of the mevalonate is considered a minimum.

[2-14C]Isovaleric acid should be metabolized to HMG-CoA
to yield the same distribution of 14C as when [4-14C]mevalonic acid is metabolized via the shunt pathway, i.e. [2-14C]2-
methylacyl-CoA would be intermediate in the metabolism
of both (1, 5). [2-14C]Acetyl-CoA would result on cleavage of
the HMG-CoA formed. Hydroxybutyric acid formed from [2-
14C]isovaleric acid would, therefore, be expected to have label
in carbons 2 and 4 in the same ratio as that observed in carbons 1 and 3 when [5-14C]mevalonate was administered and
was the case. [4-14C]Isovaleric acid is its metabolism.

[2,6-14C]mevalonic acid via the shunt pathway. In accord with
this, the greater activity in carbons 1 and 3 when [5-14C]mevalonate was administered, not being apparent.

These studies have been made under the condition of di-
abetic ketosis, since our tracing of the pathway depends upon
the isolation of hydroxybutyric acid. While the contributions
of the shunt pathway to mevalonate’s metabolism appear to vary depending on the conditions (36–38), the reactions com-
prising the pathway presumably are the same under differing
conditions.

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