Circulating Alanine Production and Disposal in Healthy Subjects

R. H. Chochinov, M.D., K. Perlman, M.D., and J. A. Moorhouse, M.D.,
Winnipeg, Manitoba

SUMMARY

Circulating-alanine production and disposal rates were estimated in eight healthy postabsorptive subjects by means of U-^{14}C alanine and U-^{14}C glucose infusions. The mean circulating-alanine production rate was 368 ± S.E.M. 28 μmol/min. · 1.8². Approximately 50 per cent of circulating-alanine carbon exchanged rapidly with that of circulating lactate. Approximately 30 per cent of circulating alanine exchanged with protein stores. Other disposal was 29 ± 2 per cent to circulating glucose and 40 ± 4 per cent to oxidation. Conclusions: (1) The carbon moieties of circulating alanine and lactate are freely exchangeable. (2) Assessment of the contribution of alanine to gluconeogenesis will depend on establishing the extent to which the precursor pyruvate carbon is derived from glycolysis or from proteolysis. (3) If the principal pyruvate precursor is glycolysis, then the principal specific function of the glucose-alanine cycle appears to be ammonia transport. DIABETES 27:287-95, March, 1978.

Alanine is formed in extrahepatic tissues by transfer of amino groups to pyruvate. Carlsten et al.[1] suggested a significance of the high splanchnic alanine removal rate[1,2] in peripherocentral ammonia transport. Mallette et al.[3] added a concept of an alanine cycle through hepatic glucogenesis.* Felig et al.[4-10] expanded this concept to that of a central role for a glucose-alanine cycle in gluconeogenesis and its control.

*In this paper the term glucogenesis refers to production of circulating glucose from all sources, that is glycogenolysis, glucose recycling, and gluconeogenesis. The term gluconeogenesis refers to the production of glucose de novo from noncarbohydrate precursors.

From the Endocrine and Metabolism Laboratory, Health Sciences Centre, and the Departments of Physiology and Medicine, University of Manitoba, Winnipeg, Manitoba, Canada. R3E 0Z3.

Address reprint requests to Dr. R. H. Chochinov, Room G449, Health Sciences Centre, 700 William Avenue, Winnipeg, Manitoba, Canada. R3E 0Z3.

Accepted for publication September 26, 1977.

Peripheral and splanchnic arteriovenous alanine differences are much higher and much more responsive to fasting and to exercise than are those of other glucogenic amino acids.[8] However, Felig et al.[5] have pointed out that an alanine cycle through glucose, while providing for ammonia transport, is otherwise analogous to the Cori cycle in not providing net substrate for glucogenesis de novo, and that for gluconeogenesis to occur, pyruvate must be formed from noncarbohydrate precursors. Felig and Wahren[7] estimated from alanine-lysine arteriovenous difference ratios that 70 per cent of the effluent alanine from leg and forearm muscle is glucose-derived.

One purpose of the present work was to question whether the concept that alanine has a special role in gluconeogenesis may have arisen from an ambiguity as to its origin. How much circulating alanine arises from protein, and how much by equilibration with the large circulating-lactate pool through the alanine aminotransferase and lactate dehydrogenase reactions?

This and other aspects of circulating alanine metabolism in postabsorptive man were studied by means of the infusion of radiolabeled alanine and glucose.

SUBJECTS AND METHODS

Subjects

The characteristics of the eight healthy subjects are given in table 1. Six were from an outpatient minor-surgery clinic and two from a nearby recreational center. None had evidence of a metabolic disorder except that four were obese. None had a family history of diabetes, and all had a fasting blood glucose level below 95 mg./dl. All were over age 40, as directed by the Atomic Energy Commission of Canada. Informed consent was obtained.

Isotope Infusions

Minor medications and alcohol were omitted for 48

TABLE 1

Characteristics of all subjects

Subject	Age	Sex	Surface area ($m.^2$)	% Optimal weight	FBS (mg./100 ml.)
N.S.	45	F	1.7	110	78
M.T.	45	F	1.7	157	70
C.H.	54	M	1.7	102	82
J.G.	54	M	2.1	133	94
H.S.	60	F	1.6	103	84
W.M.	68	F	2.0	150	88
H.L.	70	F	1.7	132	74
A.H.	83	F	1.4	100	91

hours before the start of an experiment. The subject maintained his usual activities and diet but was requested to eat a cheese or meat sandwich and drink a glass of milk at 2330 hours the evening before to establish consistency with previous studies.[11] He rested for one-half hour before the start of the infusion. During this period an indwelling catheter was inserted into a forearm vein and a blood sample was obtained.

U-^{14}C Alanine

At 0700 hours an eight-hour constant infusion of 80 μCi. of U-^{14}C alanine (99.7 per cent purity; New England Nuclear) diluted in about 190 ml. of normal saline was begun through the venous catheter. Blood samples were drawn at minutes 0, 120, 180, 240, 300, 345, 390, 435, and 480 through an indwelling catheter placed in a superficial vein of the opposite forearm. Each sample consisted of 12 ml. of heparinized blood for determination of stable† and radioactive plasma alanine levels and of the stable blood glucose level, and of 5 ml. added to 0.15 N $ZnSO_4$ for determination of the radioactive blood glucose level. Stable and radioactive lactate levels were measured in the heparinized plasma of subjects N.S., C.H., W.M., and J.C. In subjects J.G., C.H., M.T., and H.L. an additional 6 ml. of clotted blood per sample was taken for analysis of plasma albumin-specific activity. In each experiment expired air was collected in a Douglas bag for seven-minute periods beginning at minutes 55, 110, 170, 225, 285, 350, 410, and 470.

Expired-air samples were collected every morning for the next two weeks in subjects A.H. and C.Y. The experiment in C.Y. took place during protocol development and was otherwise unsatisfactory. Daily 24-hour urine samples were obtained throughout this two-week period.

†"Stable" in these experiments connotes the nonradioactive moiety.

U-^{14}C Glucose

Glucose turnover and oxidation rates were determined with a primed infusion of 10 μCi. of U-^{14}C glucose beginning at 0830 hours by the method previously described.[11] This procedure followed the U-^{14}C alanine infusion by at least three weeks, at which time the residual counts in the protein-free filtrate were negligible. Subject A.H. declined to return for a second test, and in subject J.G. the radiolabeled glucose infusion was technically unsatisfactory. In them the glucose turnover rate was estimated on the basis of its relationship to the prevailing blood glucose level.[11]

Radioiodinated Serum Albumin

The four subjects in whom plasma albumin studies had been made during the radiolabeled alanine infusion were given 2 μCi. of radioiodinated human serum albumin by a single injection at the end of the radiolabeled glucose infusion in order to determine the size of the intravascular albumin pool.[12]

ANALYTIC METHODS

Alanine

Analyses of radioactive and of stable alanine were performed on a Technicon amino acid analyzer by a modification of the NC-1 method. Ten milliliters of whole blood was added to a polyethylene centrifuge tube containing three drops of heparin solution, 1,000 USP units per milliliter. The tube was covered with Parafilm, mixed by inversion, and centrifuged at 10,000 rpm in a refrigerated centrifuge. Four milliliters of the plasma was transferred to another centrifuge tube containing 120 mg. of sulfosalicylic acid. The contents were mixed on a Vortex mixer and centrifuged at 10,000 rpm. The protein-free filtrate was removed and stored at $-20°$ C.

At time of analysis the amino acids were separated by absorption into type "A" resin.[13] One and one-half milliliters of protein-free filtrate and 1.0 ml. type "A" resin were shaken for one-half hour and centrifuged and the supernatant was removed. The resin was then washed three times with 1 ml. 0.1 N HCl. The supernatant and washings were saved for lactate analysis. Another 1 ml. of 0.1 N HCl was added to the washed resin and the mixture transferred in small volumes of buffer A (0.2 N sodium citrate buffer, pH 2.875) to a 0.6-cm.×75-cm. chromatographic column packed to a height of 40 cm. with Technicon chromobeads type "B" resin. One milliliter of 2.5 mM taurine standard in 20 per cent sucrose was added and the column carefully filled with buffer A. Elution

of the amino acids was carried out with buffer B (0.2 N sodium citrate buffer, pH 3.20). The vertical arm of a stream divider from the column was connected by 0.034-inch polyethylene tubing to a fraction collector set for three-minute fractions. Approximately two thirds of the effluent stream went to the fraction collector and one third to the analytic system. This ratio was determined accurately for each run. A 0.020-inch sample tube was used in the analytic system instead of the usual 0.033-inch tube. A single colorimeter with a 570-mm. filter and a 15-mm. light-path cuvette was used. Alanine eluted after about two hours. Stable alanine was estimated in the usual manner against the taurine internal standard. The samples containing alanine from the fraction collector were counted in Bray's solution in a Nuclear Chicago liquid scintillation counter. No radioactivity was found in the fractions containing the other amino acids, confirming an earlier observation.[14] The total recovery rate of this procedure, determined by analyzing plasma samples with added U-^{14}C alanine, was 59 ± 3 per cent (n=10). The recovery rate from plasma samples with added U-^{14}C alanine put directly through the column without resin washing was 98.5 ± 4 per cent (n=10), so that the loss occurred at this step. Its magnitude was consistent, and it did not affect the estimate of specific activity. Coefficients of variation of the results from two sets of triplicate samples were 6 per cent and 3 per cent.

The level of counts in the U-^{14}C alanine infusate was determined by counting an aliquot in Bray's solution.

Glucose

The stable and radioactive glucose in blood were measured as previously described.[11]

Carbon Dioxide

The specific activity and production rate of expired carbon dioxide were determined as previously described.[11]

Lactate

Lactate was isolated from the resin washes by the column chromatographic method of Kreisberg, Pennington, and Boshell.[15] The eluate was neutralized, flash-evaporated, and redissolved in 5 ml. of 0.1 N formic acid. A 3-ml. aliquot was taken for the determination of radioactivity. A 1.0-ml. aliquot was diluted to 5 ml. and the stable-lactate level measured by the method of Hohorst.[16]

Albumin

Albumin was isolated from 1.0 ml. of serum on a Sephadex G-200 column.[17] The fractions containing the albumin were desalted and concentrated to a volume of approximately 1 ml. Aliquots were used for protein determination by the biuret reaction,[18] radioactivity determination by liquid scintillation counting, and a check of isolation specificity by paper electrophoresis (albumin content = 92 ± S.E. 0.3 per cent, n=61).

RESULTS

An example (subject N.S.) of the results of a U-^{14}C alanine infusion is shown in figure 1. Specific activities of plasma alanine and lactate reached equilibrium by 120 minutes after the start of the infusion. The specific activities of plasma glucose and of expired carbon dioxide curved toward a plateau over the eight-hour period. The level of this plateau was estimated by applying tangents to the visual line of best fit and extrapolating to zero the linear plot of the slopes of these tangents against specific activity. These actual and estimated equilibrium specific activities were used to calculate the circulating alanine production rate and the disposal rates of alanine to glucose, lactate, and carbon dioxide in the following manner:

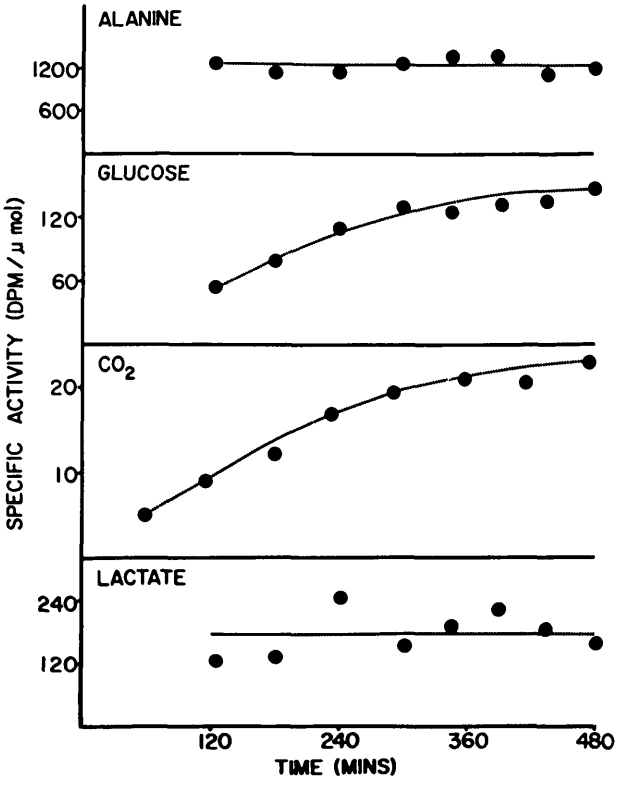

FIG. 1. An example (subject N.S.) of the results from a constant U-^{14}C alanine infusion.

1. Alanine production rate:

$$= \frac{\text{U-}^{14}\text{C alanine infusion rate (dpm/min.)}}{\text{alanine equilibrium specific activity (dpm/}\mu\text{mol/min.)}}$$

$$= \frac{354{,}433}{1{,}282}$$

$$= 280\ \mu\text{mol/min.}$$

The alanine production rate in the eight subjects correlated significantly with body surface area [alanine production (μmol/min.) = 476 × surface area ($m.^2$) − 489; $r = 0.80$, $p < 0.02$] but not with per cent ideal weight ($r = 0.31$, $p > 0.4$). This suggests that, as a function of body size, the alanine production rate is related to lean body mass rather than to the presence of obesity.[19] Alanine production rates are normalized to a surface area of 1.8 square meters.[11]

2. Per cent of glucose-C derived from alanine-C:

$$= \frac{\text{glucose equilibrium specific activity (dpm/}\mu\text{mol)} \div 6}{\text{alanine equilibrium specific activity (dpm/}\mu\text{mol)} \div 3} \times 100$$

$$= \frac{26.3}{427.3} \times 100 = 6.2\%$$

In the glucogenic pathway, pyruvate is carboxylated to oxaloacetate, which is then decarboxylated at carbon-4 and phosphorylated to form phosphenolpyruvate.[20,21] Oxaloacetate is in equilibrium with the symmetric molecule fumarate,[22] and therefore carbons 1 and 4 of oxaloacetate become randomized. The result is that glucose formed from alanine may have four, five, or six carbons labeled; the mean was five. Therefore, the adjusted value is:

3. Per cent of glucose-C derived from alanine-C:
   = % of glucose-C derived from alanine-C × 6/5
   = 6.2 × 6/5 = 7.4%

4. Amount of glucose-C derived from alanine-C:
   = % glucose from alanine × glucose production rate (μmol/min.)
   = 0.074 × 480
   = 37 μmol/min.

The calculation of the circulating glucose production and oxidation rates from the data from the radiolabeled glucose infusion has been described previously.[11] Because of the 1:2 ratio of their carbon content, the molar conversion rate of alanine to glucose is equal to twice the rate of formation of glucose from alanine. Therefore:

5. Amount of alanine-C directed to glucose-C:
   = 2 × 36
   = 72 μmol/min.

As explained above, one sixth of the original alanine carbon atoms entering this reaction are replaced in the dicarboxylic-acid shuttle.

6. Per cent of alanine-C to glucose-C:

$$= \frac{\text{amount of alanine-C to glucose-C } (\mu\text{mol/min.} \times 100)}{\text{alanine production rate } (\mu\text{mol/min.})}$$

$$= \frac{72 \times 100}{280} = 26\%$$

7. Per cent of carbon dioxide derived from alanine-C:

$$= \frac{\text{CO}_2 \text{ equilibrium specific activity (dpm/}\mu\text{mol)} \times 3 \times 100}{\text{alanine equilibrium specific activity (dpm/}\mu\text{mol)}}$$

$$= \frac{26.3 \times 3 \times 100}{1{,}282}$$

$$= 6.2\%$$

The factor 3 is the carbon ratio of alanine to carbon dioxide.

8. Amount of alanine-C appearing as carbon dioxide:
   = % CO_2 from alanine × CO_2 production rate (μmol/min.)
   = 0.062 × 9,127
   = 566 μM/min.

9. Per cent of alanine-C appearing as carbon dioxide:

$$= \frac{\text{amount of alanine-C to CO}_2 \ (\mu\text{mol/min.}) \times 100}{\text{alanine production rate } (\mu\text{mol/min.}) \times 3}$$

$$= \frac{566 \times 100}{280 \times 3}$$

$$= 69\%$$

This value includes disposal of alanine through pyruvate directly to oxidation and the disposal of alanine-derived carbon indirectly to oxidation as a result of glucogenesis. During the radiolabeled glucose infusion, 75 per cent of circulating glucose was oxidized to carbon dioxide. Therefore:

10. Per cent of alanine-derived carbon becoming carbon dioxide via glucose oxidation:
   = % alanine to glucose × 5/6 × % glucose to CO_2
   = 26 × 5/6 × 0.75
   = 16.3%

Also, one sixth of alanine-C proceeding toward glucogenesis is diverted to carbon dioxide in the dicarboxylic-acid shuttle. Therefore:

11. Per cent of alanine-derived carbon becoming

carbon dioxide via the dicarboxylic-acid shuttle:

$$= \% \text{ of alanine to glucose} \times 1/6$$
$$= 26 \times 1/6$$
$$= 4.3\%$$

12. Per cent of alanine-C oxidized directly:

$$= \% \text{ alanine to } CO_2 - (\% \text{ alanine-C to } CO_2 \text{ via glucose} + \% \text{ alanine-C to } CO_2 \text{ via dicarboxylic-acid shuttle})$$
$$= 69 - (16.3 + 4.3)$$
$$= 48.4\%$$

The fraction of circulating lactate derived from circulating alanine was calculated in a manner analogous to equation 2. It was 16 per cent.

Figure 2 shows the specific activity of serum albumin during the U-^{14}C alanine infusion in subject J.G. It did not begin to plateau, because of the large size and slow turnover rate of the albumin pool. The loss of counts from the albumin pool during the period of the experiment being negligible, its slope reflects the entry rate of counts from the alanine pool into the albumin pool. Therefore:

13. Entry rate of alanine-C into the albumin pool:

$$= \frac{\text{slope of albumin specific activity (dpm/}\mu\text{mol/min.)} \times \text{intravascular-albumin pool size (}\mu\text{mol)}}{\text{alanine equilibrium specific activity (dpm/}\mu\text{mol)}}$$
$$= \frac{2.26 \times 3{,}136}{797}$$
$$= 9\ \mu\text{M/min.}$$

14. $$\frac{\%\text{ of an alanine-C to albumin (}\mu\text{mol/min.)} \times 100}{\text{alanine production rate (}\mu\text{mol/min.)}}$$
$$= \frac{9 \times 100}{530}$$
$$= 1.7\%$$

The asymptotic values for the cumulative appearance of alanine-derived radiolabeled carbon in expired carbon dioxide over the two-week period during and following the ^{14}C alanine infusion in subjects C.Y. and A.H. were 69 and 81 per cent, respectively, of the amount infused. During the first 24 hours, 3 per cent and 2 per cent, respectively, of the labeled carbon appeared in the urine of these subjects. No significant renal excretion occurred after that time. The balance of the isotope is believed to reside in body protein, from which it will undergo slow recycling and excretion.

The mean results from all the subjects are shown in table 2.

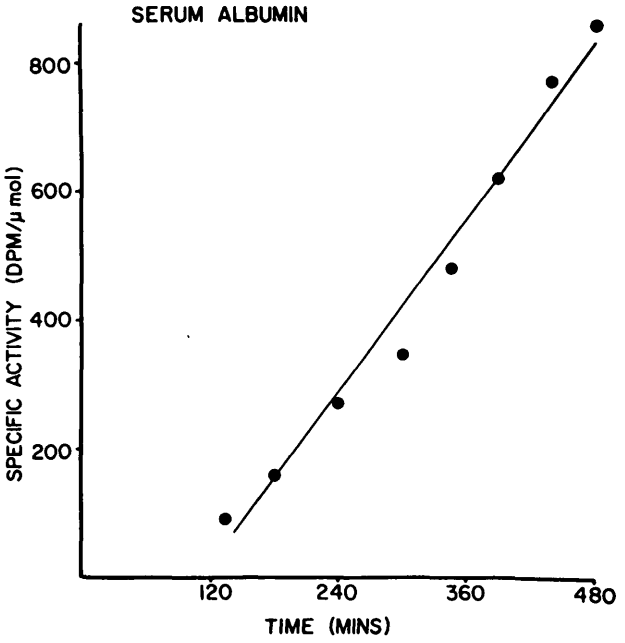

FIG. 2. An example (subject J.G.) of the appearance of radiolabeled carbon in serum albumin during a constant U-^{14}C alanine infusion.

DISCUSSION

Alanine Production

The mean circulating alanine production rate of 368 μmol/min. · 1.8 m.^{2} in the postabsorptive state was similar to that of glucose. Both rates are somewhat higher in younger subjects.[23,24] The circulating-lactate turnover rate[25] is about three times that of alanine.

Whole-blood alanine-specific activity was not measured in these experiments. Therefore the possibility of an additional exchange of alanine between blood cells or platelets and tissues[26] not influencing the di-

TABLE 2

Mean (± S.E.M.) production rates and disposal of circulating alanine

Plasma levels (μmol/ml.)	
Alanine	0.25 ± 0.01
Glucose	4.9 ± 0.09
Production rates (μmol/min. · 1.8m.^{2})	
Alanine	368 ± 28
Glucose	466 ± 19
Disposal (%)	
Alanine to glucose	29 ± 2
Glucose from alanine	11 ± 1
Alanine to CO_2	
Obligatory via oxaloacetate	5 ± 0.4
Obligatory via glucose	15 ± 1
Nonobligatory	40 ± 4
Alanine to serum albumin	1.4 ± 0.3
Lactate from alanine	16 ± 1

lution in venous plasma of the infused alanine isotope cannot be assessed. It seems unlikely that under equilibrium conditions this would be so, and the exchange of isotopic alanine between the formed elements of the blood and the splanchnic bed, at least, has been shown to be quantitatively minor.[24]

Alanine to Glucose

Twenty-nine per cent, or approximately 368 × 0.29 = 105 μmol/min. · 1.8 m.^{2} of circulating alanine entered circulating glucose. Net hepatic alanine uptake appears to be about 150 μmol/min.‡ (calculated from the data of Felig et al.[26]: average arterial-hepatic venous difference 92 μmol per liter; average arterial-portal venous difference −54 μmol per liter; average hepatic blood flow 1.12 liters per minute; approximate fraction of hepatic blood flow via hepatic artery 20 per cent). Therefore probably about 105/150 = 70 per cent of the net hepatic alanine uptake enters into glucogenesis; most of the remainder probably enters into proteogenesis[28-30] (see below).

Eleven per cent of circulating glucose arose from circulating alanine. This is similar to previous estimates[4,8,23] with one exception.[24] The principal source of circulating glucose in the postabsorptive state is glycogen.[31]

Alanine Oxidation

Sixty per cent of circulating alanine carbon was recovered as carbon dioxide. The corresponding estimate for circulating lactate is 80 to 85 per cent.[32] The respective estimates are consistent if allowance is made for the 28 per cent of alanine that is removed from substrate cycling into protein synthesis (see below). Forty per cent of alanine underwent oxidation directly, the remainder indirectly through glucogenesis.

Alanine to Protein

The fraction of circulating alanine that entered serum albumin was 1.4 per cent, representing approximately 368 × 0.014 = 5 μmol/min. · 1.8 m.^{2}. The approximate total alanine requirement for serum albumin synthesis is 10 μmol/min. (serum albumin replacement rate 202 mg./kg./day,[12] 62 alanine residues per molecule of albumin[33]). These relative values are consistent with the estimate that in the postabsorptive state about one half of the amino acids for hepatic protein synthesis are derived from hepatic protein catabolism.[34,35]

Serum albumin synthesis comprises about 5 per cent of total body protein synthesis.[36] Serum albumin and total body protein contain a similar fraction of alanine residues,[34] with probably a similar relative contribution from circulating alanine.[34,35,37] Thus, it can be suggested that approximately 1.4/0.05 = 28 per cent of circulating alanine participates in body protein synthesis. This value is consistent with the asymptote for the cumulative appearance of the radiolabeled alanine carbon in expired carbon dioxide of about 75 per cent. It also is consistent with the estimate of Felig and Wahren[7] from peripheral lysine to alanine arteriovenous difference ratios that 28 to 33 per cent of circulating alanine is derived from protein, the synthesis and breakdown rates of protein being in approximate equilibrium in the postabsorptive state.

Alanine-lactate Exchange

Sixteen per cent of circulating lactate was derived from circulating alanine. The circulating-lactate production rate in man being about 1,100 μmol/min.,[25] this is equivalent to approximately 1,100 × 0.16 = 175 μmol/min. Therefore, about 175/368 = 50 per cent of circulating alanine was transformed swiftly into lactate. An extensive alanine-to-lactate transfer has been noted previously.[14] It precedes and should be distinguished from eventual alanine disposal to glucogenesis, oxidation, and proteogenesis. Lactate is a circulating intermediate. A simultaneous transfer of carbon from lactate to alanine is predictable from the near-equilibrium state[3,38,39] and the ubiquity[39,40] of the alanine-aminotransferase reaction. Such a carbon exchange will produce isotope dilution but not an arteriovenous difference (figure 3), and, thus, the discrepancy between the net (see above) and the present alanine production rates (150 and 368 μmol/min., respectively) is quantitatively consistent with it. These considerations lead to a concept of one equilibrated system related to net peripherocentral carbon and amino recycling. To dwell on the so-called glucose-alanine cycle is to omit lactate, which is quantitatively the principal component of this system, in addition to the other moieties, pyruvate, glutamate, and alpha ketoglutarate.

Total Alanine Disposal

Total circulating-alanine disposal in the postabsorptive state is summarized in figure 4. *Early* means for over minutes to an hour or two, *intermediate* means for over several hours, and *ultimate* means for over hours to weeks. These phases are a continuum. About 30 per cent of circulating alanine departs from short-term recycling and oxidation into long-term recycling through protein stores. About 50 per cent, or in fact,

‡Because the liver is the only tissue that exhibits net alanine uptake[3,7,27] this value can also be viewed as the net alanine production rate.

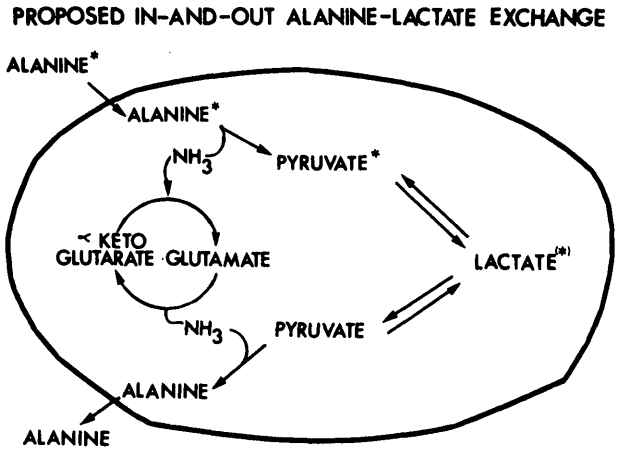

FIG. 3. The alanine-lactate carbon exchange (see text). The symbol * indicates the radiolabel in the entering carbon moieties. The symbol (*) indicates that the large lactate pool is seen both as the major recipient of labeled carbon and the major donor of unlabeled carbon in the exchange. The deamination-amination equilibrium is catalyzed by the enzyme alanine aminotransferase (EC2.6.1.2). This mechanism produces isotope dilution but not an arteriovenous difference in plasma alanine concentration. It provides union between the alanine and the lactate cycles.

70 per cent of the nonproteogenic fraction of circulating alanine transfers swiftly to the lactate pool, the turnover rate of which is $1,100/368 \times 0.7$ = fourfold greater. The remainder is entering glucogenic or oxidative pathways during the early phase. Intermediate alanine disposal directly or through lactate is about 30 per cent to circulating glucose, 40 per cent to carbon dioxide, and 3 per cent to urinary excretion. One hundred per cent of the infused radiolabeled alanine is accounted for. Ultimate disposal is oxidative.

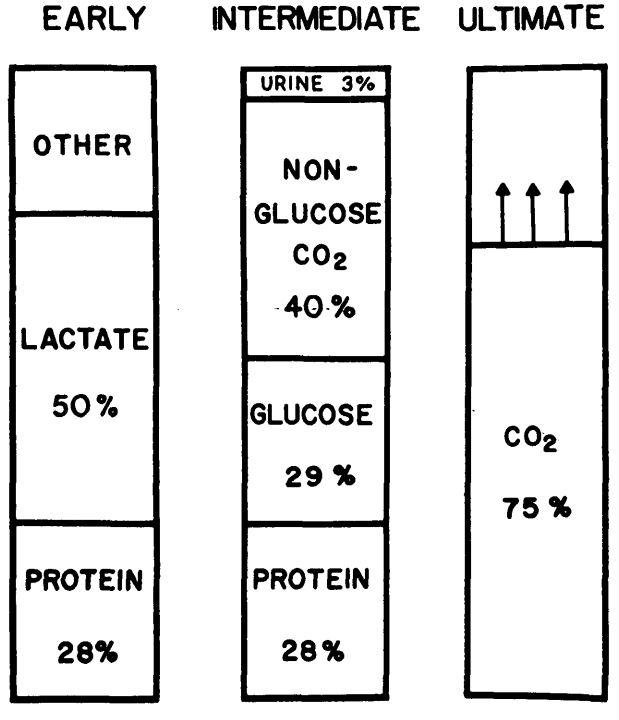

FIG. 4. Total circulating alanine disposal. See text.

Sources of Circulating-alanine Carbon

The estimate from the present and other data (see above) for the proximate sources of circulating alanine carbon is about 30 per cent from alanine preformed in protein, leaving about 70 per cent to come from amination of pyruvate. It has become controversial whether this pyruvate is derived principally from proteolysis or from glycolysis, an important question relating to whether circulating alanine participates principally in gluconeogenesis or in glucose recycling. Garber et al.[39,41] and Goldstein and Newsholme[42] recently have reproposed the view[43,44] that the precursor pyruvate is derived mostly from protein. Their main evidence is that in isolated rat skeletal muscle, alteration of glycolysis rates over a wide range were not rate-controlling for alanine release, whereas the addition of several amino acids to the medium was rate-controlling. In our opinion this finding is of interest but is not definitive, because the alanine carbon source was not isotopically traced. Although suggestive, there was not direct evidence in their experiments that the released alanine carbon originated from the added amino acids, which may therefore have acted as amino donors. Their observations at the present time appear to be consistent with the possibility that amino rather than pyruvate availability is rate-limiting to tissue alanine formation.[39] There is alternative evidence that supports glycolysis as the principal carbon source for alaninogenesis. Odessey et al.[45] found that at least 60 to 80 per cent of alanine carbon recovered from muscle isolated from glycogen-depleted rats appeared to originate from medium ^{14}C-labeled glucose at physiologic concentration. The relevance of this in-vitro finding to intact man is supported by the observation that exercise sharply increases alanine release in health[7] but not in patients who lack muscle glycogen phosphorylase.[46] In agreeing that at this time the carbon source for new alanine formation is unsettled, one must suggest that in that case the carbon source of lactate also is unsettled, since the carbon moieties of lactate and of alanine exchange through their common precursor, pyruvate (see above). Until now glycolysis generally has been accepted as the principal lactate carbon source.[25]

The (Lactate-alanine)-glucose Cycle

Our concept of the physiologic relationships between glucose, lactate, and alanine in the postabsorptive state is illustrated in figure 5. The alanine and lactate cycles exchange carbon freely, although they have specific functions with respect to ammonia transport and redox control, respectively. The central intermediary is pyruvate. Alanine and lactate capacitate pyruvate-to-glucose recycling. With respect to this recycling it seems not conceptually useful to separate the alanine from the Cori cycle, since there is free exchange of carbon from one to the other.

In this concept with respect to glucogenesis, circulating alanine has two sources and two roles: About 30 per cent is preformed alanine from protein stores and about 70 per cent is pyruvate-derived. The role of this latter component depends on the pyruvate source, the controversy over which (see above) needs to be settled. If, on the one hand, the principal source is glycolysis, then this alanine component is not an amino acid in the functional sense of being derived from stored protein or the amino acid pool, but rather would be viewed as circulating pyruvate that happens to be carrying an amino radical. It would not be regarded as participating significantly in gluconeogenesis any more than is lactate, because its principal carbon source would be glucose either from the circulation or from glycogen. If, on the other hand, the principal precursor-pyruvate source for this alanine component is proteolysis, then it does participate in gluconeogenesis.

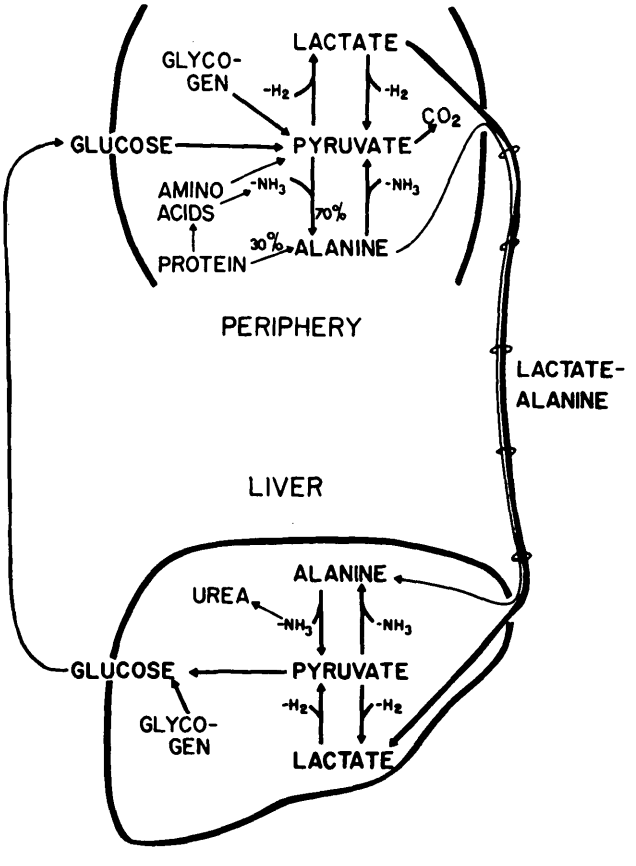

FIG. 5. The (lactate-alanine)-glucose cycle. See text for detailed description.

Our present opinion is that the principal specific physiologic function of the glucose-alanine cycle is not glucogenesis but ammonia transport.[1,3]

ACKNOWLEDGMENTS

The method for the simultaneous analysis of stable and radioactive alanine was developed under the direction of Mr. D. R. Grant, Chief Technologist, Endocrine and Metabolism Laboratory, Health Sciences Centre.

This work was supported by Operating Grant MT 811 from the Medical Research Council of Canada.

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