Regulation of plasma free fatty acid turnover

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In a general way it has been considered that the concentration of FFA in the plasma is indicative of the rate at which FFA is being transported or, more loosely speaking, lipid is being mobilized. However, it is clear that this need not necessarily be true. For example, facilitation of FFA uptake by a particular hormone or agent might lower plasma FFA concentration even though the rate of FFA production were to remain the same or even to increase. Indeed, such facilitation is seen in isolated adipose tissue in vitro. Here both glucose alone and glucose plus insulin stimulate the over-all uptake of fatty acids from the medium (3, 4). Also, turning to the comparable process of glucose transport through the circulating blood, the rate of glucose uptake is well known not to be related to glucose concentration in any simple way because a variety of agents and hormones influence the readiness with which glucose is taken up at any given plasma glucose concentration.

The present studies were undertaken to evaluate, in the whole animal, the relationship between FFA concentration and FFA uptake and so to throw light on the manner in which FFA concentration and turnover are regulated. Palmitate tagged with C14, infused intravenously at a constant rate, was used to measure FFA turnover rate under a variety of experimental conditions that brought about variations of FFA concentration over a 30-fold range. Certain additional experiments were performed that add support to the concept that FFA is a major vehicle for lipid transport.

MATERIALS AND METHODS

Animals and experimental materials. Adult normal dogs, trained to lie quietly on the operating table, were used in these experiments. The AL series dogs were kept on a diet previously described (5); the B and J series dogs were kept on a diet of five parts commercial dog pellets and one part commercial canned dog food.

The C14-palmitate (palmitate-1-C14, New England Nuclear Corp., Boston, Mass., palmitate-6-C14, Isotope Specialties Co., Burbank, Calif.) was prepared for infusion by dissolving its potassium salt in CO2-free distilled water and diluting to the desired volume with CO2-free
distilled water, or with autologous serum, or with an approximately 0.5% solution of bovine serum albumin (75-100 mg albumin/mg palmitate) in physiological saline. The specific activity of the palmitate used was such that the weight of palmitate being infused was always less than 0.5% of the production rate of endogenous plasma free fatty acids by the dog.

Sodium pentobarbital, norepinephrine, and dichlorodimethyl ether were used as supplied by drug manufacturers. Glucose, oleic acid, and the reagents used for analyses were chemically pure compounds. Solvents used for lipid extraction were redistilled before use. Bovine serum albumin, glucagon-free insulin, and bovine growth hormone (Somar A, lot R-50109) were obtained as purified protein preparations.

The respiratory mask and techniques for collection of the CO₂ of the respired air have been described (6).

Experimental procedure. After the dog had been arranged with its head either in the respiratory mask for CO₂ collection or in a chemical hood when CO₂ was not collected, a continuous infusion of C₁₄-palmitate solution was begun via either a cephalic or saphenous vein using a syringe-drive constant-infusion pump (Harvard Apparatus Co., Inc.) delivering a few tenths of a milliliter per minute through an indwelling (PE-50) polyethylene catheter (Intramedic tubing, Clay Adams, Inc., N. Y.).

Blood samples were taken in some experiments from a femoral artery exposed under local (procaine) anesthesia but in most experiments were obtained from the jugular vein either by direct venipuncture or by means of an indwelling (PE-190) polyethylene catheter kept patent by means of a slow drip of physiological saline. The various methods of blood collection gave equivalent results. In experiments in which blood samples were taken from the jugular vein, a saphenous vein was used for C₁₄-palmitate infusion.

Injections or continuous infusions of agents affecting FFA concentration were given via saphenous or cephalic veins.

Blood samples were taken at intervals for measurement of plasma FFA concentration and specific activity; in some instances plasma glucose concentrations were also measured. Blood samples were collected in heparinized syringes and were chilled in a crushed-ice bath. For FFA measured. Blood samples were collected in heparinized syringes and were chilled in a crushed-ice bath. For FFA measured. Blood samples were collected in heparinized syringes and were chilled in a crushed-ice bath. For FFA measured. Blood samples were collected in heparinized syringes and were chilled in a crushed-ice bath. For FFA measured. Blood samples were collected in heparinized syringes and were chilled in a crushed-ice bath. For FFA measured. Blood samples were collected in heparinized syringes and were chilled in a crushed-ice bath. For FFA measured. Blood samples were collected in heparinized syringes and were chilled in a crushed-ice bath. For FFA measured. 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PLASMA FREE FATTY ACID TURNOVER

FIG. 1. FFA concentrations, specific activities, and mean turnover rates (calculated for 30-min intervals) in a 21.3-kg dog in the postabsorptive state during a palmitate-1-C\textsuperscript{14} infusion (exp. 1, Table 1). Respiratory CO\textsubscript{2} specific activities at 30-min intervals are also given; mean total CO\textsubscript{2} output was 60.4 mgC/min.

FIG. 2. FFA concentrations, specific activities, and mean turnover rates (calculated for 30-min intervals) in a 16.5-kg dog in the postabsorptive state during a palmitate-6-C\textsuperscript{14} infusion (exp. 3, Table 1). Respiratory CO\textsubscript{2} specific activities at 30-min intervals are also given; mean total CO\textsubscript{2} output was 52.8 mgC/min.

FFA to be added to this pool as its total FFA content (the turnover time) is about 2.7 min in the present series of experiments (see Fig. 3). There is very little difference in turnover time between the highest and lowest FFA concentrations encountered because of the proportionality between FFA inflow-outflow rate and plasma FFA concentration.

It can be shown that the following relationship exists between time, specific activity, and C\textsuperscript{14} infusion rate for a pool having a turnover time of 2.7 min:

\[
\overline{S_A_t} = \overline{S_A_0} e^{-\frac{t}{30t}} + \frac{F}{g} \left(1 - e^{-\frac{t}{30t}}\right)
\]

where

- \(\overline{S_A_t}\) = FFA specific activity at time \(t\), \(\mu\text{eq}/\mu\text{eq}\)
- \(\overline{S_A_0}\) = initial FFA specific activity, \(\mu\text{eq}/\mu\text{eq}\)

It can be seen that as the infusion \(F\) is continued for an infinite time the value of \(e^{-\frac{t}{30t}}\) goes to zero and \(\overline{S_A_0}\) becomes \(\frac{F}{g}\) without regard to the initial specific activity, \(\overline{S_A_0}\). If it is wished to know how long it will take for the specific activity of the FFA pool to reach 99.9% of its equilibrium value of \(\frac{F}{g}\), substitution in equation 2 again gives 18.6 min.

Thus for practical purposes the priming dose necessary in the case of C\textsuperscript{14}-glucose experiments (6) can be dispensed with in measurement of FFA turnover in the dog if a period of about 20 min is allowed to elapse between initiation of C\textsuperscript{14}-palmitate infusion and the measurement of FFA specific activity. Under these conditions the FFA specific activity is independent of the specific activity existing 20 min previously and the inflow-outflow rate of FFA can be calculated from the simple relationship given in equation 1.

Variations in FFA turnover in the normal unanesthetized dog. Fig. 1 and 2 show the changes in FFA concentration, FFA specific activity, and FFA turnover during several hours of observation in two normal unanesthetized dogs. The experiment represented in Fig. 1 was carried out using palmitate-1-C\textsuperscript{14} and that in Fig. 2 using palmitate-6-C\textsuperscript{14}. In each case random variations in plasma FFA concentration were seen during the experiment. When mean FFA turnover rates are calculated for successive 30-min periods as shown in Fig. 1 and 2 it is seen that these rates vary by as much as ±15% from the mean value for the whole observation period. This variability is to be considered in evaluating the results given in Tables 1 and 2 for observation periods of similar short duration.
Changes in FFA turnover under conditions that raise or lower FFA concentration. Tables 1 and 2 summarize the data used in the preparation of Fig. 3. FFA turnover rates ranged from 10.1 to 26.8 μEq/kg/min in the nine experiments on eight unanesthetized normal dogs in the postabsorptive state (exp. 1, 2, 3, 4a, and 5a in Table 1; exp. 11a, 12a, 13a, and 14a in Table 2). These points are denoted in Fig. 3 by open circles to show the dependence in these animals of FFA turnover on FFA concentration.

Sodium pentobarbital (Nembutal) anesthesia lowered plasma FFA concentration and reduced FFA turnover to a range of 2.3-8.0 μEq/kg/min in four experiments on three dogs (exp. 6a, 6b, 7, and 8a in Table 1). These points are denoted by open triangles in Fig. 3. Intravenous glucose infusion at 10 mg/kg/min during Nembutal anesthesia reduced plasma FFA concentration and lowered turnover further to a range of 2.1-3.0 μEq/kg/min (exp. 6b, 9, and 10 in Table 1). In one experiment (exp. 12c in Table 2) in an unanesthetized dog, glucose infusion lowered FFA concentration and turnover, but not greatly. The glucose experiments are denoted by open squares in Fig. 3.

Insulin, infused at a rate (.025 unit/kg/hr) not sufficient to have much effect on plasma glucose concentration, had only a small lowering effect on FFA concentration and turnover (exp. 4b in Table 1). Insulin at twice this dosage rate (exp. 5b in Table 1) lowered plasma glucose concentration to 52-56 mg% in 60-90 min and lowered FFA concentration and turnover by one-third. A complicating factor in insulin infusion experiments is the response of the dog to hypoglycemia; this is considered fully in a separate communication (to be published). This response includes a restoration of FFA concentration and turnover to the preinsulin level or higher and may occur during the course of a prolonged insulin infusion. This phase of the two insulin experiments of Table 1 is given in Table 2 (exp. 4c and 5c) where it is described as “response to hypoglycemia.” The points in Fig. 3 for the early phase of insulin action are denoted by closed squares and those for the later phase by closed circles.

The effect of longer periods of fasting on FFA concentration and turnover is shown in Table 2 (exp. 11b and 11c). A 42-hr and 114-hr fast did not elevate these values much above the 18-hr fasting level, which for this particular animal was at the extreme upper limit of the range of normals. The longer fasting points are denoted by open hexagons in Fig. 3.

Growth hormone injected intravenously at 3 mg/kg body wt is very effective in elevating FFA concentration and turnover in the course of a few hours (exp. 12b in Table 2). The growth hormone point is denoted by a closed hexagon in Fig. 3.

FIG. 3. A plot of FFA concentration against FFA turnover for all the experiments reported in Tables 1 and 2. The regression line has the formula \( Y = 18.97X - 0.43 \); the sample SD of the regression coefficient is 4.35; \( P < .001 \) for the null hypothesis that there is no dependence of uptake rate on concentration. The meanings of the various symbols used to represent individual points are given in the text. The point represented by the star enclosed in a circle is that derived from the sodium oleate experiment (Fig. 4) and was not used in calculating the regression line.

FIG. 4. Plasma FFA concentrations (solid line) observed during changes in FFA turnover under conditions that raise or lower FFA concentration. The i.v. infusion of sodium oleate solution at 50 μEq/min in a 14.8-kg dog. Endogenous FFA production was maintained at a low level by Nembutal anesthesia and continuous i.v. insulin infusion. The dashed line represents the expected rise in FFA concentration based on the assumption that there is zero turnover of FFA during the oleate infusion, i.e., no endogenous FFA production and no utilization of the original FFA or of the infused oleate. A plasma volume equal to 5% of the body wt. of the dog was used in this calculation.
endogenous FFA production was not influenced by the turnover at the observed FFA concentration of continuous insulin infusion. The FFA turnover rate prior whose endogenous FFA concentration and turnover rate following initiation of the infusion (exp. 8c and r3b in Table 3) were denoted in Fig. 3 by closed point for FFA turnover in Fig. 3 can be established at the FFA flow into the plasma was about 6.8 pEq/min, a new oleate infusion so that total exogenous plus endogenous body wt (exp. r4b and r4c in Table 2). epinephrine and DC1 are denoted in Fig. 3 by closed triangles.

FFA concentration during oleate infusion of 0.3 μEq/ml (see Fig. 4). This point is designated in Fig. 3 by a star in an open circle, and can be seen to fall reasonably close to the line that relates FFA concentration to turnover as determined by the results of the C14-palmitate experiments. This represents confirmation by nonisotopic means that FFA turnover rates as measured with C14-palmitate are of the proper order of magnitude.

Norepinephrine infusion at 0.25-0.50 μg/kg/min raised FFA concentrations and turnover rates manyfold over an observation period extending from 18 to 65 min following initiation of the infusion (exp. & and 13b in Table 2). A drug that blocks certain actions of sympatho-amines, dichloroisoproterenol (DCI), was nevertheless very potent in elevating FFA concentrations and turnover rates when given intravenously at 3 mg/kg body wt (exp. 16b and 14b in Table 2). The points for norepinephrine and DCI are denoted in Fig. 3 by closed triangles.

Fig. 4 represents the results of an experiment in which plasma FFA was elevated by the infusion of a sodium oleate solution at a rate of 3.59 μEq/kg/min into a dog whose endogenous FFA concentration and turnover rate were at low levels due to Nembutal anesthesia and a continuous insulin infusion. The FFA turnover rate prior to oleate infusion was not measured. However, the usual turnover at the observed FFA concentration of 0.2 μEq/ml can be seen from Fig. 3 to be about 3.3 μEq/kg/min. The dashed line in Fig. 4 represents the course that the plasma FFA concentration would have taken if there were no FFA turnover at all and no uptake of the infused oleate. The observed course of the FFA concentration is shown by the solid line in Fig. 4, which demonstrates that the infused oleate was removed quite effectively from the circulating FFA pool. Assuming that the endogenous FFA production was not influenced by the oleate infusion so that total exogenous plus endogenous FFA flow into the plasma was about 6.8 μEq/min, a new point for FFA turnover in Fig. 3 can be established at the FFA concentration during oleate infusion of 0.3 μEq/ml (see Fig. 4). This point is designated in Fig. 3 by a star in an open circle, and can be seen to fall reasonably close to the line that relates FFA concentration to turnover as determined by the results of the C14-palmitate experiments. This represents confirmation by nonisotopic means that FFA turnover rates as measured with C14-palmitate are of the proper order of magnitude.

Rate at which FFA leaving plasma is converted to CO2. Fig. 1 and 2 show the specific activity of the expired CO2 during the continuous intravenous infusion, into unanesthetized dogs in the postabsorptive state, of palmitate-1-C14 and palmitate-6-C14, respectively. There is no significant difference between the results of these two experiments, although in the one case the C14 is in the terminal carboxyl group of the long-chain fatty acid and goes to the carboxyl group of the acetate derived during metabolic degradation and in the other case the C14 is well down the length of the chain and goes to the methyl group of acetate. It is concluded that the appearance of C1402 from a single position (1 or 6) of palmitate is a fair criterion for the metabolic degradation of the whole molecule to CO2.
The major contribution of the present study is the demonstration that the turnover rate of plasma FFA is related in a quantitative manner to the prevailing plasma FFA concentration. The highly significant \( P < 0.001 \) linear regression of turnover on plasma concentration is illustrated in Fig. 3. A similar dependence of the rate of FFA uptake by the liver on the plasma FFA concentration of the blood circulating through that organ has been demonstrated recently by Fine and Williams (17) and by MC Elroy et al. (18).

One aspect of FFA turnover is uptake, and since FFA concentration solely by changing the rate of FFA production rate controls the FFA concentration at an unchanging FFA concentration must equal uptake.

The effects of FFA concentration of the various agents and conditions used in the experiments described here are in accord with previous findings. The effect of the new drug dichloroisoproterenol on FFA concentration has not been described previously.

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under a wide variety of conditions to evaluate FFA turnover simply by measuring plasma FFA concentration. It appears that the special case represented by adipose tissue in vitro in which there is facilitation of FFA uptake by glucose alone and by glucose plus insulin (3, 4) is not paralleled by a facilitation or blockage of over-all FFA uptake by the whole animal under various conditions that change plasma FFA concentration.

With regard to the use of C¹⁴-palmitate to measure FFA turnover, it has been observed frequently that when the introduction of tagged palmitate is stopped the FFA specific activity falls rapidly in accord with the measured rate of FFA turnover for only a short time. Subsequently the FFA specific activity falls at a much slower rate. This finding was confirmed in the present studies, and as a practical matter, when successive C¹⁴-palmitate infusions were carried out, it was found necessary to wait 90 min after terminating one infusion before beginning another. By that time the FFA specific activity had fallen to 5%–10% of its steady-state value during the previous infusion.

In this connection Bates and Olson (19) prepared a slowly turning over C¹⁴¹ FFA in vivo by oral administration of C¹⁴-palmitate to a donor dog 24 hr prior to collection of blood for injection into a recipient dog. An explanation for their findings is that C¹⁴¹ had been incorporated into a minor FFA constituent differing in origin and metabolic rate from the major FFA constituents. In fact, Meinertz and Dole (20) describe arachidonic acid as being such a minor FFA constituent. Although such cycling of C¹⁴¹ into a minor slow-moving component may have been a factor in the present studies, another explanation also suggests itself for the delayed fall in FFA specific activity that was seen following termination of C¹⁴-palmitate infusion. Wasserman et al. (21) have described an extravascular pool of albumin that mixes slowly (over an 8-hr period in the dog) with intravenously injected T¹¹¹-tagged albumin. If FFA accompanies albumin into such an extravascular albumin pool then FFA tagged with C¹⁴-palmitate would build up slowly in the extravascular albumin during a C¹⁴-palmitate infusion and would return slowly to the circulating albumin pool after termination of the C¹⁴-palmitate infusion.

Several aspects of the present work bear on the concept of the rapidity of turnover of the major components of FFA and their importance in energy metabolism. The intravenous infusion of a bulk amount of sodium oleate was shown to result in its disappearance from the plasma FFA at a rate consistent with expectations from C¹⁴-palmitate experiments. Also elevation of the endogenous FFA level by norepinephrine infusion was followed by a prompt decline in FFA level on termination of the infusion. Because of uncertainty as to the duration of norepinephrine action this result cannot be quantitatively evaluated but demonstrates that endogenous FFA can be taken up "rapidly." Finally, the appearance of the C¹⁴¹ of infused palmitate in the respiratory CO₂ was found to occur at a rapid rate.

It is interesting to compare FFA and glucose with regard to their respective contributions to the total energy metabolism. As shown in the present work, 91%–93% of the total CO₂ output of the resting unanesthetized dog in the postabsorptive state comes from fatty acids promptly after their uptake from the plasma by the utilizing tissues. Previous findings in dogs under identical conditions (15) have shown that about 14% of the total CO₂ output arises promptly from glucose after uptake by the tissues. Both of these circulating metabolic fuels taken together thus account for about 40% of the total metabolic CO₂ that is produced. As to the extent to which these metabolites, once they are taken from the plasma, are burned to CO₂, the present studies show that 18%–27% of the FFA taken up goes promptly to CO₂ whereas previous studies (15) have shown that about 40% of the glucose taken up from the plasma goes promptly to CO₂.

Dichloroisoproterenol was kindly supplied by Dr. I. H. Slater, Lilly Research Laboratories. Trypsin treated insulin, low in glucagon content, was kindly supplied by Dr. O. K. Behrens of Lilly Research Laboratories. "Novo" insulin was kindly supplied by Dr. P. Schambyc, Novo Tčrapeálisk Laboratorium A/S, Copenhagen, Denmark. Bovine growth hormone (Somar A lot R-50109) was a gift from the Endocrine Study Section, National Institutes of Health.

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