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RELATIONSHIP IN MAN BETWEEN PLASMA FREE FATTY ACIDS AND MYOCARDIAL METABOLISM OF CARBOHYDRATE SUBSTRATES*

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Summary Significant negative linear relationships were found between myocardial extraction of glucose, lactate, and pyruvate and arterial free fatty acid (F.F.A.) concentration in 17 healthy resting fasting men. This suggests that F.F.A. can suppress the myocardial uptake of glucose in man as they do in the isolated perfused rat heart, and that this may be due at least in part to inhibition of pyruvate dehydrogenase. These conclusions were supported by the observation in another 10 subjects that reduction of arterial F.F.A. concentration by the administration of nicotinic acid increased myocardial extraction of all 3 carbohydrate substrates.

Introduction

SEVERAL studies on the interaction between free fatty acids (F.F.A.) and carbohydrate metabolism in the isolated perfused rat heart have suggested that enhanced myocardial oxidation of fatty acids can suppress the uptake and oxidation of glucose.[1-5] On the basis of such studies it has been proposed that the higher rate of fatty-acid oxidation in diabetes mellitus and in starvation is responsible for the pattern of carbohydrate metabolism found in muscle in those conditions.[3,4]

When the isolated rat heart is perfused with a medium containing both glucose (either with or without insulin) and also a fatty acid such as octanoate, butyrate, or palmitate complexed to albumin, the uptake and oxidation of glucose is considerably less than when the fatty acid is not present in the perfusate. In this preparation fatty acids appear to produce inhibition at a number of points in the pathway of glucose metabolism (fig. 1). There is decreased membrane transport of glucose (and of the non-metabolised glucose analogue L-arabinose) (step 1) and also inhibition of glucose phosphorylation (step 2), glycolysis (step 3), and pyruvate decarboxylation (step 4).[3-7] The basic mechanism whereby fatty acids suppress intracellular glucose metabolism is related to the increase in the ratio of intracellular acetyl coenzyme A/coenzyme A which accompanies enhanced fatty-acid oxidation.[8] When the acetyl-coenzyme-A/coenzyme-A ratio rises, pyruvate dehydrogenase is inhibited (step 4)[9] and an increase in intracellular citrate concentration also occurs[8] which in turn inhibits phosphofructokinase (step 3).[4,10] Finally, an increase in glucose-6-phosphate concentration, which appears to be secondary to the phosphofructokinase inhibition, inhibits hexokinase, so that the rate of glucose phosphorylation is decreased (step 2).[3,4]

The rate-limiting step in glucose uptake may be either glucose phosphorylation or membrane transport according to the experimental conditions. In the Lagendorff isolated rat-heart preparation, performing minimal ventricular work, and perfused with high concentrations of glucose and insulin, glucose phosphorylation appears to be the rate-limiting step in glucose uptake, and the inhibition of this uptake by F.F.A. is due principally to diminished glucose phosphorylation consequent upon the increased glucose-6-phosphate concentration. However, the maximum rate of intracellular glucose utilisation in the isolated rat heart may reflect myocardial energy requirements; and if the energy requirements of the isolated heart are increased by making it perform pressure or volume work, there appears to be a marked stimulation of glucose transport and phosphorylation. Under these circumstances the principal inhibitory effect of fatty acids seems to be at the level of membrane transport of glucose.[11]

Many of the animal studies upon which the hypothesis of the suppression of glucose uptake by fatty acids is founded have been criticised for the use of relatively low glucose and high F.F.A. concentrations and high F.F.A./albumin ratios—all of which favour fatty-acid metabolism. It has been suggested, therefore, that arguments about the choice of substrate for myocardial oxidative metabolism based on isolated perfused rat-heart studies with unphysiological experimental conditions may not be directly relevant to the problem of substrate choice by the heart in vivo.[12] In order to see whether a relationship does exist in man between plasma-F.F.A. and myocardial metabolism of carbohydrate substrates similar to that which has been observed between perfusate fatty acids and the metabolism of carbohydrate substrates in the isolated perfused rat heart, we have measured the arterial concentrations and myocardial extraction of F.F.A., glucose, lactate, and pyruvate in healthy men.

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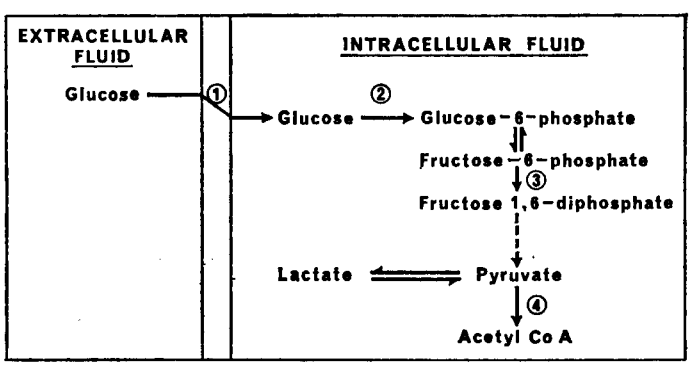

Fig. 1—Control points in glucose uptake and oxidation in heart muscle.
Rate-limiting enzymes are shown in parentheses.
1, Membrane transport.
2, Glucose phosphorylation (hexokinase).
3, Fructose 6-phosphate phosphorylation (phosphofructokinase).
4, Pyruvate decarboxylation (pyruvate dehydrogenase).

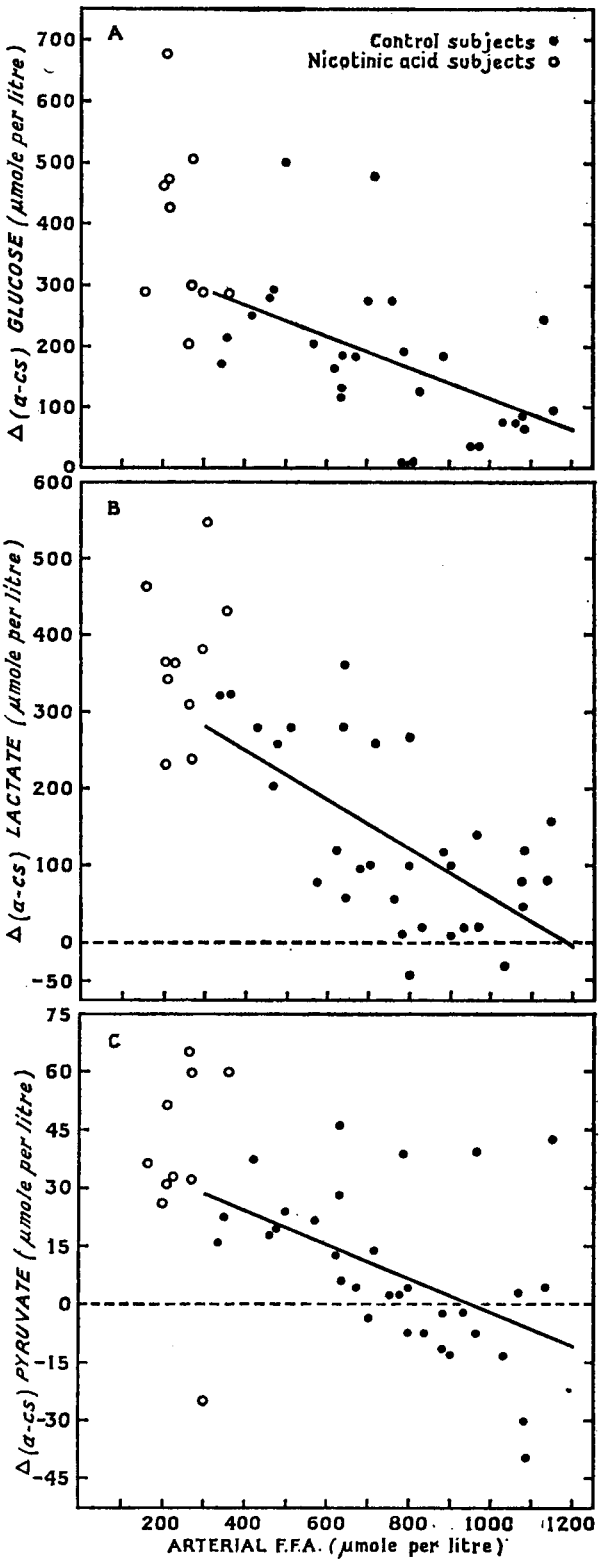

Fig. 2—Relationship between myocardial extraction ($\Delta_{(a-cs)}$) of (A) glucose, (B) lactate, and (C) pyruvate and arterial F.F.A. concentration in 17 subjects not receiving nicotinic acid (control group) and 10 subjects receiving a continuous intravenous infusion of nicotinic acid.

The regression lines have been calculated from the control group data only (see table I [1]).

Methods

27 healthy male volunteers, aged 21–58 years, were studied at rest after an overnight fast. Arterial and coronary sinus catheterisation was carried out as previously described.[13] Heparin was not administered to the subjects. Arterial and coronary-sinus plasma-F.F.A.,[14] blood-glucose,[15] blood-lactate,[16] and blood-pyruvate [17] were measured and myocardial extraction (i.e., arterial/coronary-sinus concentration difference) was calculated. In 17 subjects arterial and coronary-sinus blood samples were drawn simultaneously after the subject had been resting for 60 minutes; and in 15 of them these were taken again 30 minutes later. In 2 of these 17 subjects glucose measurements were not made for technical reasons. The remaining 10 subjects received a constant intravenous infusion of nicotinic acid in order to reduce their plasma-F.F.A. concentrations,[18] and blood samples were drawn 60 minutes after the beginning of the infusion. Multiple regression analysis was performed according to Snedecor and Cochran.[19]

Results

Fig. 2 shows the relationship between arterial F.F.A. concentration and myocardial extraction of glucose, lactate, and pyruvate. The regression and correlation analyses of these relationships are presented in table I (1). There were significant negative linear relationships between myocardial extraction of all three substrates and arterial F.F.A. concentration. There was also a significant efflux of pyruvate from the heart into the coronary-sinus blood at higher F.F.A. concentrations. The figures show that reduction of the arterial F.F.A. concentration by the administration of nicotinic acid was usually associated with much higher extraction of all three of the carbohydrate substrates.

Table I (2) shows that in those subjects not receiving nicotinic acid there was a significant positive linear relationship between myocardial extraction and arterial concentration for pyruvate, but not for glucose or lactate. Table II presents the parameters for the linear regression of myocardial extraction of the particular carbohydrate substrate (y) on both arterial F.F.A. concentration (x_1) and arterial concentration of that substrate (x_2). For all three carbohydrate substrates the negative regression of myocardial extraction on arterial F.F.A. concentration remains significant when any effect of the changing arterial concentration of the carbohydrate substrate itself is removed. In addition, when the negative effect of increasing F.F.A. concentration is removed, there is a significant positive linear relationship between lactate extraction and arterial lactate concentration.

Discussion

The negative relationship between arterial F.F.A. concentration and the myocardial extraction of glucose suggests that F.F.A. can suppress glucose uptake by the human heart in vivo, as it does in the isolated perfused rat heart. This suggestion is supported by the observation that glucose extraction was increased when F.F.A. concentration was reduced by the administration of nicotinic acid. In addition, the finding that with increasing arterial concentration of F.F.A. there was decreasing myocardial extraction of pyruvate, with actual efflux from the heart at higher F.F.A. concentrations, suggests that in vivo the inhibition of glucose uptake may be at least partly due to suppres-

TABLE I—REGRESSION AND CORRELATION ANALYSES IN THOSE SUBJECTS NOT RECEIVING NICOTINIC ACID OF MYOCARDIAL EXTRACTION OF VARIOUS CARBOHYDRATE SUBSTRATES AND (1) THE ARTERIAL CONCENTRATION OF F.F.A. AND (2) THE ARTERIAL CONCENTRATION OF THAT SUBSTRATE

y	Regression analysis			Correlation analysis		
	x	b ± S.E.M.	a ± S.E.M.	r	n	P
1						
$\Delta_{(a-cs)}$ Glucose	F.F.A.$_a$	−0·26 ± 0·08	370 ± 70	−0·51	28	< 0·01
$\Delta_{(a-cs)}$ Lactate	F.F.A.$_a$	−0·31 ± 0·07	370 ± 60	−0·62	32	< 0·001
$\Delta_{(a-cs)}$ Pyruvate	F.F.A.$_a$	−0·04 ± 0·01	41 ± 12	−0·46	32	< 0·01
2						
$\Delta_{(a-cs)}$ Glucose	Glucose$_a$	0·05 ± 0·04	−20 ± 20	0·24	28	N.S.
$\Delta_{(a-cs)}$ Lactate	Lactate$_a$	0·17 ± 0·09	20 ± 60	0·33	32	N.S.
$\Delta_{(a-cs)}$ Pyruvate	Pyruvate$_a$	0·75 ± 0·08	−30 ± 44	0·86	32	< 0·001

Where $y = bx + a$. Subscripts a and cs refer to arterial and coronary sinus respectively. $\Delta_{(a-cs)}$ = arterial/coronary-sinus difference in concentration—i.e., myocardial extraction.

TABLE II—MULTIPLE LINEAR REGRESSION ANALYSES OF MYOCARDIAL EXTRACTION OF VARIOUS CARBOHYDRATE SUBSTRATES (Y) ON ARTERIAL F.F.A. CONCENTRATION (X_1) AND ARTERIAL CONCENTRATION OF THE CARBOHYDRATE SUBSTRATE (X_2) IN THOSE SUBJECTS NOT RECEIVING NICOTINIC ACID.

y	x_1	x_2	$b_1 \pm$ S.E.	$b_2 \pm$ S.E.	a	n
$\Delta_{(a-cs)}$ Glucose	F.F.A.$_a$	Glucose$_a$	$-0{\cdot}26 \pm 0{\cdot}08^{(b)}$	$0{\cdot}05 \pm 0{\cdot}03^{(ns)}$	160	28
$\Delta_{(a-cs)}$ Lactate	F.F.A.$_a$	Lactate$_a$	$-0{\cdot}31 \pm 0{\cdot}06^{(c)}$	$0{\cdot}18 \pm 0{\cdot}06^{(a)}$	250	32
$\Delta_{(a-cs)}$ Pyruvate	F.F.A.$_a$	Pyruvate$_a$	$-0{\cdot}03 \pm 0{\cdot}01^{(c)}$	$0{\cdot}70 \pm 0{\cdot}06^{(c)}$	−7	32

Where $y = b_1x_1 + b_2x_2 + a$. Abbreviations as in table I. Superscripts indicate significance of regression coefficient: a = $P < 0{\cdot}01$; b = $P < 0{\cdot}005$; c = $P < 0{\cdot}001$; n.s. = $P > 0{\cdot}05$.

sion of pyruvate decarboxylation—a finding in keeping with the results of experiments in the isolated perfused rat heart.

It has been proposed that, since hypoxia results in accelerated glycolysis with formation of lactate from pyruvate rather than its entrance into the tricarboxylic-acid cycle, the percentage extraction of lactate by the heart is a good indicator of myocardial ischæmia in man.[20] However, the negative relationship between F.F.A. and both lactate and pyruvate extraction does suggest that F.F.A. as well as hypoxia may inhibit pyruvate decarboxylation and produce a diminished percentage extraction of lactate. Thus the arterial F.F.A. concentration should also be taken into consideration when lactate extraction is used to assess the adequacy of myocardial oxygenation in man. Since both heparin and catecholamines increase arterial F.F.A. concentrations, this is particularly important in studies in which heparin is being used as an anticoagulant during cardiac catheterisation, or in which catecholamines are being administered in an effort to provoke myocardial ischæmia.

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