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Inhibition of carnitine-acyl transferase I by oxfenicine studied in vivo with [^{11}C]-labeled fatty acids☆

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Abstract

Methods: Anesthetized pigs were studied with [^{11}C]-labeled fatty acids (FAs) with carbon chain length ranging from 8 to 16 carbon atoms, during control conditions and during inhibition of carnitine-palmitoyl transferase I (CPT I) with oxfenicine. The myocardial uptake of [^{11}C]-FAs from blood was measured together with the relative distribution of [^{11}C]-acyl-CoA between rapid mitochondrial oxidation and incorporation into slow turnover lipid pools in the heart.

Results: During baseline conditions, the fractional oxidative utilization of palmitate was almost as high as that of carnitine-independent short-chain FAs, unless the carnitine shuttle was inhibited by high levels of lactate. Inhibition of CPT I almost completely blocked the oxidative pathway for palmitic acid and reduced the fractional oxidative utilization, while the rate of oxidative metabolism of acyl-CoA was unaffected.

Conclusions: [^{11}C]-Labeled FAs allow rapid oxidation to be well separated from esterification into slow turnover lipid pools in the heart of anaesthetized pigs. The fractional oxidative utilization of [^{11}C]-palmitate serves well to characterize, in vivo, the carnitine-dependent transfer of long-chain FAs.

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1. Introduction

Long-chain saturated fatty acids (FAs) constitute the major source of energy substrates in the normoxic heart. Once activated to acyl-CoA, FAs can be degraded by β-oxidation in mitochondria and peroxisomes or stored in slow turnover lipid pools such as triglycerides and phospholipids. The transfer of acyl residues into the mitochondrial matrix relies on a carnitine-dependent transport system, which serves as the primary regulatory site for FA oxidation [1,2]. Carnitine deficiency syndromes, which may arise from genetic defects in the homeostasis of carnitine (primary) or from genetic defects in acyl-CoA metabolism (secondary), are associated with cardiomyopathy and a varying degree of contractile dysfunction [3–5]. Carnitine has also been implicated in the pathophysiology of ischemic heart disease [6–9]. Ischemia results in loss of carnitine from the myocardium [10] and accumulation of toxic levels of long-chain acyl-carnitine and acyl-CoA [11,12]. It is therefore of great interest to study the involvement of the carnitine system in humans with different types of contractile dysfunction, especially to monitor the biological effects of carnitine in vivo, that is, the transfer of acyl-CoA to the mitochondrial space. This should also allow the efficacy of therapeutic interventions such as carnitine replacement or dietary manipulations to be assessed objectively.

Earlier studies with positron emission tomography have demonstrated that [^{11}C]-labeled palmitic acid may be used to characterize myocardial FA metabolism noninvasively

☆ The purpose of this study was to evaluate carbon-11-labeled fatty acids and positron emission tomography for the study of carnitine-dependent transport of long-chain fatty acids in the heart.

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[13,14]. Analyzing the clearance of [^{11}C] from normoxic myocardium in terms of a biexponential washout, the faster component correlated with the production of [^{11}C]CO_2, indicative of β-oxidation with the formation of [^{11}C]-acetyl-CoA and subsequent oxidation to [^{11}C]CO_2 by the tricarboxylic acid (TCA) cycle. The slower component correlated with incorporation of tracer into triglycerides. Using a more elaborate four-compartment model, assessments of the rate constants of palmitate oxidation and palmitate incorporation into slow turnover processes were made [15]. The purpose of the present study was to evaluate the use of FA tracers labeled with [^{11}C] to study the enzymatic activity of carnitine-palmitoyl transferase I (CPT I), specifically the impact of CPT I inhibition by oxfenicine (*S*-4-hydroxy-phenyl-glycine) [16] on tracer performance. Studied were made in pigs using [^{11}C]-labeled saturated FA tracers ([^{11}C]-FA) with carbon chain length ranging from 8 to 16 carbon atoms. The short-chain FAs, which are essentially independent of CPT I [17], were used to highlight secondary metabolic changes along the FA oxidative pathway during CPT I inhibition.

2. Theory

The salient steps of myocardial FA metabolism [18] are outlined in Fig. 1, which illustrates the routes of the [^{11}C] label. Fatty acids are either degraded by β-oxidation within the mitochondrial matrix or incorporated into the slow turnover pools of triglycerides or phospholipids. Transport of long-chain acyl-CoA into mitochondria is facilitated by the carnitine-dependent transferase-translocase system at the mitochondrial membrane. Each turn of the β-oxidation sequence results in the formation of acetyl-CoA and the loss

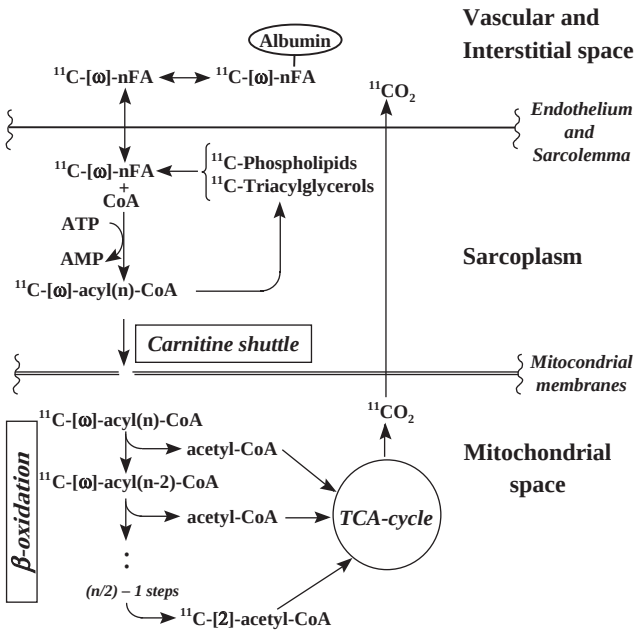

Fig. 1. Schematic representation of ^{11}C-FA metabolism in the myocardium. See text for details.

of two carbon atoms from the acyl-residue carbon chain. Thus, labeling with [^{11}C] in the ω position of an FA with an even number (n) of carbon atoms [^{11}C]-acetyl-CoA is released after (n/2)−1 turns, with label in the methyl position. [^{11}C]-acetyl-CoA is subsequently oxidized in the TCA cycle with formation of [^{11}C]CO_2, which is readily cleared from the intracellular space and distributed in the carbonate pool of the body.

2.1. ^{11}C-FA uptake

The transfer of FAs from blood to the intracellular pool of acyl-CoA is realized by a reversible transport of FAs across the cell membranes and an essentially irreversible esterification to acyl-CoA (FA activation). Such a process may be represented by a two-compartment model and analyzed in terms of the apparent distribution volume of FAs (V_D) and the net transfer rate constant K_T [19]. This was made by a least-squares fit to the equation:

$$c^*_M(t) = V_D c^*_i(t) + K_T \int_0^t c^*_i(\tau)d\tau \quad (1)$$

where asterisk (*) denotes the radioactive label, $c^*_M(t)$ the amount of [^{11}C] held by the irreversible compartment at time t and $c^*_i(t)$ the arterial input function of tracer. Eq. (1) applies only after steady state has been established for the transfer of [^{11}C]-FAs between blood and tissue and prior to any significant clearance of [^{11}C]CO_2 from the myocardium. Once the transfer rate constant had been derived, the amount of [^{11}C]-FA extracted at time t [$c^*_E(t)$] may be calculated as

$$c^*_E(t) = K_T \int_0^t c^*_i(\tau)d\tau \quad (2)$$

The total amount of tracer extracted (Q^*_E) is obtained when tracer has been cleared from plasma [$c^*_E(t)$=0].

2.2. [^{11}C]-FA retained in slow turnover lipid pools

The turnover of triglycerides and phospholipids by the heart is far slower than the oxidative turnover [14]. The amount of [^{11}C]-FAs accumulating in the pools of esterified lipids (Q^*_R) was measured under the assumption that there was no significant hydrolysis of ^{11}C-labeled triglycerides or phospholipids during the study period. Q^*_R was obtained as the amount of radioactivity retained in the myocardium when the oxidative pathway had been cleared from [^{11}C] metabolites by the end of the study (Fig. 2). Apart from an early back-diffusion of unmetabolized FAs, [^{11}C]CO_2 is the only labeled compound released in significant amounts from the myocardium [20,21]. The amount of tracer oxidized to [^{11}C]CO_2 may thus be obtained as $Q^*_E - Q^*_R$ and the fractional oxidative utilization of FAs extracted calculated as $(1 - Q^*_R/Q^*_E)$. The clearance rate of [^{11}C]-labeled metabolites (K_{ox}) was calculated by a monoexponential least-squares fit, using the latter part of the washout curve when

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