Elevated Hepatic Gluconeogenesis in Lung Cancer and Relation with Weight Loss
as observed by $^{31}$P MRS with L-Alanine Infusion

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Introduction

Profound alterations in host metabolism have been observed in lung cancer patients with weight loss. One of the proposed mechanisms is deranged host metabolism, especially amino acid utilization for endogenous glucose production. Previous observations showed elevated gluconeogenesis from alanine in weight-losing lung cancer patients. 3

$^{31}$P-MRS with L-alanine infusion, has been used to study gluconeogenesis within the liver in vivo. We previously reported elevated levels of phosphomonoesters (PME) in weight-losing lung cancer patients which could not be stimulated any further with alanine infusion. 2 It remains unclear, however, whether these alterations were caused by the presence of lung cancer or weight loss.

The purpose of this study was to monitor hepatic gluconeogenesis in lung cancer patients with and without weight loss. We used $^{31}$P MRS of the liver in combination with L-alanine infusion under steady state conditions.

Methods

Subjects: Lung cancer patients with weight loss (12+2%, mean ± SEM; CaWL, n=9) and without weight loss (CaWS, n=12), without liver metastases, as confirmed by CT / ultrasound, and healthy control subjects (C, n=12) were studied after an overnight fast. All subjects had normal liver function tests.

$^{31}$P MRS: Hepatic $^{31}$P MR spectra were obtained at 2 T using a Siemens Magnetom Vision and a 16 cm surface coil placed lateral to the liver in the mid-axillary plane. 1D CSI (1x4 phase-encoded matrix, field of view 40x40 cm) was applied on a transverse slice of 4 cm centered on the coil, yielding volumes of 40x10x4 cm$^3$. Data were collected with a 640 µs shaped RF pulse and a 135° flip angle in the center of the coil, using a repetition time (TR) of 1 s. Spectra were obtained sequentially at 3 min. intervals prior to and during a primed-constant infusion of L-alanine for 90 minutes (dose 1.4-2.8 mmol/kg BW + 2.8 mmol.kg$^{-1}$.hr$^{-1}$). Spectra were analyzed by Siemens Numaris-3 software. Results are given as mean ± SEM and reported relative to total MR-detectable phosphate.

Biochemistry: Blood samples were taken at baseline and analyzed for metabolite concentrations.

Results

Plasma glucose and alanine concentrations were similar in CaWL, CaWS and C. Baseline PME levels were significantly elevated in WL lung cancer patients (CaWL, 10.5 ± 1.0%, mean ± SEM; CaWS, 6.7 ± 0.5%; C, 8.2 ± 0.7%; P<0.001), whereas ATP in these patients was significantly reduced as compared to both CaWS and C (CaWL, 9.5 ± 0.9%; CaWS, 12.6 ± 0.8%; C, 12.1 ± 0.7%; P<0.05). The P/ATP ratio, as a measure of intracellular energy status, was significantly elevated in CaWL as compared with both CaWS and C (1.1 ± 0.2 vs. 0.7 ± 0.1 and 0.7 ± 0.1, respectively, P=0.03). Changes in liver metabolites during L-alanine infusion are presented in Figure 1. At 45-90 min. of L-alanine infusion, PME had increased by 50 + 16% in C and 87 ± 31% in CaWS (area under the curve, P<0.01). No change in PME was observed in CaWL (7 ± 9%). ATP levels declined during L-alanine infusion in both CaWL and CaWS as well as in C (CaWL, -21 ± 7% and CaWS, -13 ± 5%; P<0.05; C, -12 ± 5%; P<0.01). Changes observed in P/ATP ratios during L-alanine infusion did not reach statistical significance (CaWL, 21 ± 12%; CaWS, 13 ± 15%; C, -6 ± 11%).

The degree of weight loss was correlated with PME levels at baseline (Pearson, r=-0.59, P<0.001) and with changes in PME during L-alanine infusion (r = 0.49, P = 0.01).

Discussion

PME concentrations increased significantly in both CaWS and C during continuous L-alanine infusion, while no such change occurred in CaWL. These L-alanine-stimulated changes in PME were inversely correlated with the degree of weight loss, implicating that altered hepatic gluconeogenesis as observed by $^{31}$P MRS is related with weight loss and not with lung cancer per se.

L-alanine infusion reduced ATP levels in both lung cancer patients and C. This may be caused by the increased energy demand during gluconeogenesis which apparently is not completely matched by ATP resynthesis in the mitochondria. In C and CaWS some recovery of ATP occurred after 60 min of alanine infusion. The fact that this was not observed in CaWL would suggest an impaired ATP recovery in these patients.

References