Quantitation of Hepatic Gluconeogenesis in Cancer Cachexia by use of $^{31}$P MRS and L-Alanine Infusion

S. Halfwerk,1,2 P. E. Sijens,1 J. W. O. van den Berg,2 M. Oudkerk,1 P. C. Dagnelie1,2
1 Department of Diagnostic Radiology, Daniel den Hoed Cancer Center, Rotterdam, and
2 Institute of Internal Medicine II, Erasmus University Rotterdam, The Netherlands

Introduction

Cancer cachexia is a wasting syndrome characterized by increased protein breakdown and aberrant loss of body weight. It occurs in up to 80% of all cancer patients and contributes to the morbidity and mortality in this disease. One of the proposed mechanisms is deranged host metabolism, especially amino acid utilization for endogenous glucose production. We previously reported increased levels of liver phosphomonooesters (PME) as detected by $^{31}$P-MRS in cancer patients with weight loss. Elevated PME was highly prognostic for weight loss and decreased survival. Since PME contains contributions from intermediates of hepatic glycolysis / gluconeogenesis, L-alanine / $^{31}$P MRS has been used to obtain quantitative information on hepatic gluconeogenesis in vivo.2

The purpose of this study was to obtain quantitative information on hepatic gluconeogenesis in weight-losing lung cancer patients. We used $^{31}$P MRS of the liver in combination with L-alanine infusion under steady state conditions.

Methods

Subjects: Weight-losing lung cancer patients (mean weight loss ± SD: 15 ± 5 %) without liver metastases, as confirmed by CT / ultrasound, and healthy control subjects were studied after an overnight fast. All subjects had normal liver function tests.

Spectroscopy: 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 (1×4 phase-encoded matrix, field of view 40×40 cm) was applied on a transverse slice of 4 cm centered on the coil, yielding volumes of 40×10×4 cm³. Data were collected with a 640 μs shaped RF pulse and a 135° flip angle in the center of the coil, using repetition time (TR) of 1 s. Spectra were obtained prior to and continuously during a primed-constant infusion of L-alanine for 90 minutes (dose 2.8 mmol/kg BW + 2.8 mmol/kg.hr). Spectra were analyzed by Siemens Numaris-3 software. Results are given as mean ± SEM.

Biochemistry: Blood samples were taken at baseline and during alanine infusion, and analyzed for glucose, alanine, insulin, and glucagon.

Results

L-alanine infusion significantly increased PME levels (peak area) by 24 ± 9 % (area under the curve, P < 0.03) in healthy controls (Figure 1). Maximum PME-levels were reached within 40 minutes and remained high during the continuous L-alanine infusion. In contrast, weight-losing lung cancer patients already had significantly increased PME-levels at baseline, confirming previous results, but did not show any change after an i.v. L-alanine load (4 ± 12%, P= 0.95). During alanine infusion, β-ATP decreased significantly (Fig. 1) in both controls and weight-losing cancer patients; however, the fall in ATP was twice as much in cancer patients than in controls. Pt showed a similar decreasing trend in both groups which was only statistically significant in the weight-losing lung cancer patients (-17 ± 6%, P < 0.05).

Plasma glucose concentrations were similar at baseline in both healthy controls and weight-losing lung cancer patients (6.2 ± 0.03 mM in PWL vs. 6.3 ± 0.04 in C). Alanine infusion, however, caused a significant decrease in plasma glucose in the cancer patients (5.6 ± 0.02; P < 0.01) while in the control subjects plasma glucose remained constant.

Discussion

This study confirms increased hepatic PME-levels in healthy control subjects following the infusion of alanine, reflecting increasing concentrations of gluconeogenic intermediates.2 Interestingly, in weight-losing lung cancer patients baseline PME was already high and did not change during alanine infusion. It therefore seems that gluconeogenesis is already maximal at baseline and cannot be stimulated any further by the infusion of a gluconeogenic amino acid in these patients.

The fall in β-ATP during an i.v. L-alanine load in both weight-losing lung cancer patients and healthy controls may be caused by an energy deficit occurring in the liver.3 Gluconeogenesis is an energy consuming process that can exhaust intracellular ATP supply. Weight-losing lung cancer patients may thus not be able to compensate for the use of ATP during alanine-stimulated gluconeogenesis. This would lead to a greater energy deficit within the hepatocytes and could explain why PME does not increase any further. A lack of conversion of alanine into glucose could also partly explain the decrease in plasma glucose in these patients.4

References