PRELIMINARY REPORT

^{31}P Magnetic Resonance Spectroscopy of Human Liver in Elderly Patients: Changes According to Nutritional Status and Inflammatory State

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Magnetic resonance spectroscopy (MRS) was used to determine the phosphorylated metabolite content in the liver of elderly patients in various nutritional states: normal, with protein deprivation, and with acute inflammatory syndrome. ^{31}P-MRS investigations were performed at 1.5 T, and localized liver spectra were recorded using a two-dimensional chemical shift imaging sequence. Comparison to control spectra recorded on 10 healthy volunteers (age, 30.5 ± 2.1 years) showed that the aging process does not significantly modify ^{31}P-MRS liver spectra. Patients with protein deprivation exhibited a higher value than controls for the phosphomonoesters/nucleoside triphosphates (PME/NTP) ratio ($P < .05$). This increase was not due to the decrease of NTP, since the ratio of inorganic phosphate to NTP (P_i/NTP) remained constant. A decrease in the phosphodiesters to NTP (PDE/NTP) ratio ($P < .04$) contributed to the observed increase in the PME/PDE ratio ($P < .01$). In contrast, no significant difference in ^{31}P-MRS spectra was found between elderly patients with hypoalbuminemia associated with inflammatory syndrome and the control group. We conclude that elderly patients with protein deprivation displayed changes in the level of phosphorylated metabolites in the liver that were not observed in the case of inflammatory syndrome despite lower serum albumin (Alb) concentrations.

PROTEIN ENERGY MALNUTRITION (PEM) is common in hospitalized and chronically institutionalized elderly people. The prevalence of PEM in nursing homes is approximately 30% to 60%.[1] Currently, serum albumin (Alb) and thyroxine-binding prealbumin (TBPA) are identified as the best biochemical indicators of visceral protein status: Alb is a liver secretory protein with low turnover, whereas TBPA displays a high turnover. Alb is widely used as an indicator of PEM because it is easily included in routine biochemical investigations. During inflammatory syndrome, Alb concentration decreases in elderly patients but not in young adults.[2] The question is whether Alb could be considered a good indicator of chronic protein deprivation in the elderly during the inflammatory process.

^{31}P two-dimensional chemical shift imaging[3] can record phosphorylated metabolites from liver that are present in concentrations higher than approximately 0.5 mmol/L. This allows evaluation of high-energy compounds, nucleoside triphosphates (NTP), inorganic phosphate (P_i), phosphomonoesters (PME), and phosphodiesters (PDE) in the human liver in vivo. This method, which is noninvasive, in contrast to biopsy and in vitro studies, provides metabolic information from localized regions of liver.

The aim of this study was to assess the influence of aging and to evaluate the respective role of PEM and/or acute inflammatory syndrome on phosphorylated metabolite content in the human liver.

SUBJECTS AND METHODS

The elderly patients were compared with 10 healthy young volunteers (control group). The elderly subjects were 14 inpatients of the Geriatric Centre. They were free of any liver disease, had average alcohol consumption, and did not take any hepatotoxic drug. The erythrocyte sedimentation rate (ESR) in the first hour was measured by the Westergren method. Concentrations of Alb (normal range, 35 to 45 g/L) and TBPA (normal range, 0.10 to 0.40 g/L) were determined by latex immunonephelometry (BNA; Behring, Rueil-Malmaison, France). Patients were measured and weighed. Quetelet's body mass index ([BMI] normal range, 18 to 23 kg/m^2) was the anthropometric variable. Routine clinical and biological examinations were performed for selection of patients without any liver disease. Patients were separated into two groups according to the level of Alb. Studies including Alb as a marker of PEM set the threshold value at either 30 or 35 g/L.[1] The cutoff point between normal and reduced albumin concentration was set at 32 g/L (group I, Alb > 32 g/L; group II, Alb < 32 g/L). The value of 32 g/L was chosen to enhance the difference, if any, between groups I and II. We separated group II into two subgroups: without (group IIa) and with (group IIb) inflammatory syndrome. Because the upper limit of the normal range increases with aging,[4] we set the ESR cutoff point at 50. Patients in groups I and IIb were clinically selected as being normally healthy: they came from the community, had no cognitive impairment, were not depressed, and had no history of recent weight loss.

Magnetic Resonance Spectroscopy Investigations

Patients were examined 1 to 2 hours after a normal lunch.

Magnetic resonance spectroscopy (MRS) measurements were performed on a whole-body SP63 Siemens magnet (Siemens, Erlangen, Germany) operating at 1.5 T. Spectra were acquired using transmit-receive, home-built surface coils tuned at 63.6 MHz and 25.7 MHz for ^{1}H and ^{31}P measurements, respectively. The subjects were in ventral decubitus, the liver region being close to the surface coils. A proton image using the proton surface coil was first obtained. Spectral localization was performed with a two-dimensional chemical shift imaging sequence. This sequence consisted of one slice-selective radiofrequency pulse followed by two phase-encoding gradients. It resulted in a 8 × 8 matrix, which

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Submitted January 18, 1996; accepted April 8, 1996.

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0026-0495/96/4509-0003$03.00/0

corresponds to 64 voxels of 39 cm^3 (3.125 × 3.125 × 4 cm) each. We obtained a spectrum from each voxel. We used a 225° pulse in the center of the ^{31}P coil, which allowed signal detection up to 100 mm depth. Spectra were acquired with a 1-second repetition time. To analyze the data, we considered the spectrum from the voxel centered on the axis of the coil. Phosphocreatine resonance, characteristic of muscle tissue and absent in the liver, was not detected or was indistinguishable from the noise level. Resonance area calculations were performed, and the ratio of each area to the βNTP area was considered for analysis.

Statistical Analysis

We compared the spectroscopic data for each elderly group with the data for a control group using a distribution-free test, because of the small number of subjects in each group. A Mann-Whitney rank-sum test was performed. Results are expressed as the mean ± SD.

RESULTS

Fourteen elderly subjects were included in this study: five in group I, five in group IIa, and four in group IIb. They were of similar age (I, 80.4 ± 6.3 years; IIa, 85.8 ± 4.1; IIb, 85.8 ± 4.1). BMI was in the normal range in groups I and IIa (I, 22.5 ± 7.1 kg/m^2; IIa, 21.0 ± 1.9); patients in group IIb were all overweight (BMI, 30.5 ± 2.3). Patients in each group were clearly separated by Alb level (I, 35.3 ± 1.5 g/L; IIa, 31.3 ± 0.4; IIb, 27.8 ± 2.5). We observed widespread concentrations of TBPA in each group (I, 0.27 ± 0.04 g/L; IIa, 0.17 ± 0.3; IIb, 0.21 ± 0.11). The control group consisted of 10 adults aged 30.5 ± 2.1 years with BMI in the normal range (22.8 ± 2.2 kg/m^2).

Figure 1 shows ^{31}P-MRS liver spectra of a patient from group I and a patient from group IIa. Calculated metabolic area ratios for control subjects and elderly patients are reported in Table 1. Patients in group IIa exhibited higher values for the PME/NTP ratio. This increase could be due to a lower NTP level. However, P_i /NTP ratio was maintained constant. Consequently, we interpreted this PME/NTP increase as an increase of PME. Furthermore, a slight decrease of the PDE/NTP ratio contributed to the increase of the PME/PDE ratio in the same group.

The metabolic ratios in patients from group I, considered well-nourished, were not statistically different from those in control subjects. The PME/NTP ratios of patients with inflammatory syndrome were slightly higher than those of the control group. We observed more variation in the PME/NTP ratio between subjects in the elderly group than in the control group.

DISCUSSION

We expected to find in the group of undernourished patients an alteration of the P_i/NTP ratio, as described in the case of rat liver in a fasting situation by Cunningham et al,[5] in which fasted livers had a 2.3-fold increase in the Pi/NTP ratio; no other changes were described in their study. Here, no evidence of an alteration in energy compounds was demonstrated in normal or malnourished elderly patients. In fact, the patients involved in this study were not in a fasting situation; we explored the effects of chronic PEM, particularly chronic protein deprivation.

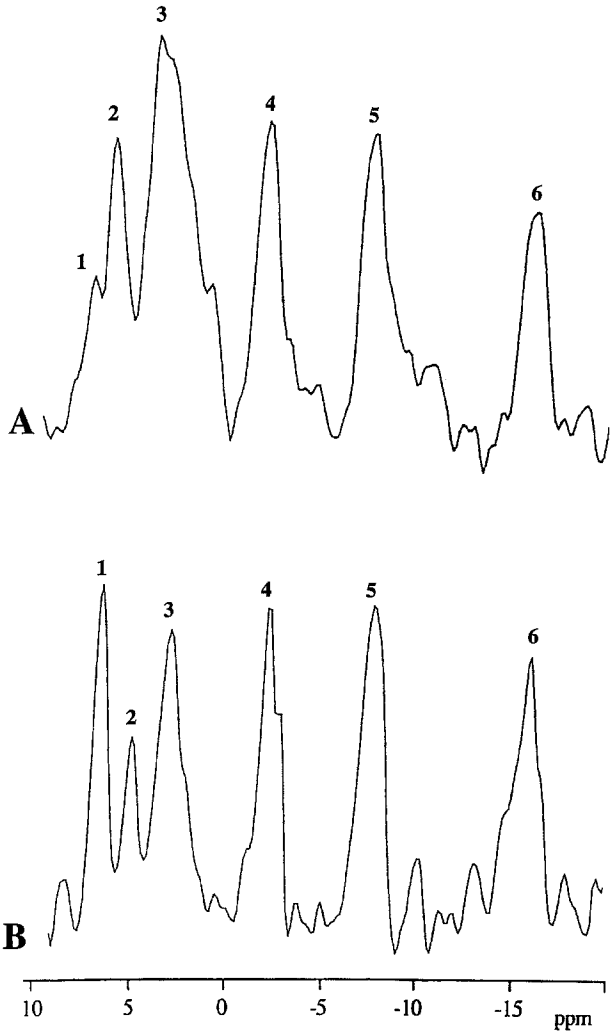

Fig 1. ^{31}P-MRS localized liver spectra of patients from group I (A) and group IIa (B). Peaks: 1, PME; 2, P_i; 3, PDE; 4, γ-NTP; 5, α-NTP; 6, β-NTP.

The main finding of this study is the increase of the PME/NTP ratio and the decrease of the PDE/NTP ratio in elderly patients with hypoalbuminemia but without inflammatory syndrome. Several biochemical species contribute

Table 1. ^{31}P-MRS Metabolite Area Ratios of Patients and Controls

Group	PME/NTP	PDE/NTP	P_i/NTP	PME/PDE
Control (n = 10)	0.47 ± 0.16	2.03 ± 0.72	0.64 ± 0.18	0.26 ± 0.15
I (n = 5)	0.51 ± 0.18	1.87 ± 0.88	0.69 ± 0.26	0.29 ± 0.10
IIa (n = 5)	0.72* ± 0.18*	1.22 ± 0.42†	0.62 ± 0.24	0.64 ± 0.29‡
IIb (n = 4)	0.64 ± 0.23	1.57 ± 0.24	0.525 ± 0.14	0.41 ± 0.16

NOTE. The elderly groups are defined as follows: I, normonourished; IIa, serum Alb < 32 g/L and normal ESR; IIb, low Alb and elevated ESR (>50 mm in the first hour). Data are expressed as the mean ± SD.

*$P < .05$.

†$P < .04$.

‡$P < .01$.

to the PME signal: sugar phosphate, adenosine monophosphate, and particularly compounds such as phosphorylethanolamine and phosphorylcholine.[6-7] These last two are associated with phospholipid biosynthesis. Even though the chemical shifts of the species are different, they all appeared with a broad resonance.

Data obtained in vitro[8] suggested an association between PDE resonance and endoplasmic reticulum. Newly synthesized secretory proteins accumulate on or within the rough endoplasmic reticulum, and it was thus proposed that secretory proteins are synthesized selectively in the rough endoplasmic reticulum.[9] The decrease in the PDE/NTP ratio in elderly patients with protein deprivation is consistent with these data.

Improvements in the ^{31}P-MRS technique, greater field strength, proton-decoupling spectra, and ^{13}C-MRS[10] or ^{1}H-MRS could yield further information, namely identification of the sugars, phosphorylethanolamine, and phosphorylcholine in the liver during PEM.

Our results suggest that elderly patients with protein deprivation show changes in liver ^{31}P-MRS metabolites. These changes were not observed in elderly patients with inflammatory syndrome, despite a lower concentration of serum Alb. This can be explained assuming that an early decrease of serum Alb is associated with the acute inflammatory syndrome,[2] whatever the nutritional status of the subject. The results suggest that the serum Alb value must be considered with respect to inflammatory status.

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