Intestinal Glutamine Metabolism of Patients with HIV-Infection

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INTRODUCTION

The intestinal mucosa is a major barrier against translocation of enteric bacteria to the internal compartments. Recently, it was postulated that GLN-supplementation may help to maintain the barrier function of the injured mucosa [1]. Until now, the intracellular amino-acid metabolism of the human gut has not been characterized exactly. In particular, it is not known whether or not intestinal diseases are accompanied by intracellular GLN-depletion. With the help of a new procedure for AA-analysis of mucosal biopsies [2], we were able to investigate whether the duodenal GLN-metabolism is altered in HIV-positive patients with duodenitis.

METHODS

Biopsies of duodenal mucosa were obtained during routinely performed GI-endoscopy from 6 HIV + patients with histologically proven duodenitis, and from 11 GI − patients with normal duodenum. The specimens were shock-frozen by fluid nitrogen, lyophilized and extracted with 250 ul of a 30 g/l solution of sulfosalicylic acid in 0.1 mol/l lithium citrate buffer (final pH: 2.2) containing 5 g/l dithioethanol. After centrifugation, the extracts were analysed by ion exchange chromatography in a Biotronik LC 5001 analyser (Biotronik, München, FRG). The amino-acid levels (mmol/kg dry weight) of each individual are the median concentrations of 3 parallel biopsies. Statistical differences were tested with the U-test (sign.: **—$p < 0.025$, ***—< 0.01).

RESULTS

The table lists the absolute concentrations of free amino-acids in biopsies of the duodenum, which differ between normals and HIV + patients.

Next to GLU, ASP (mean: 13.7, SD: 2.1) shows the highest levels of intramucosal free AA, without difference between normals and HIV + patients. The total essential AA make up 14% of the AA sum. The data of HIV + subjects show much higher standard deviations than that of the other patients.

DISCUSSION

Our data on the intraduodenal AA pattern confirm comparable results from rat small intestine [3] and human jejunum [4]. The intestinal GLN/GLU ratio differs completely from that of muscle and plasma with the lowest (highest) absolute and relative GLN (GLU)-levels in the duodenal mucosa. Under physiological conditions, the intestinal GLN-concentrations depend predominantly on glutaminase activity of the tissue. The specific activity is similar in duodenum, jejunum and ileum, but much lower in stomach, cecum and colon of the rat [5]. As we stated elsewhere [2], this is also the fact in man. The altered mucosal GLU-levels of HIV + patients of comparable disease-stage have also significantly increased plasma glutamate levels [6]. The reasons for these imbalances are not known so far. We also do not know whether HIV-negative persons with duodenitis show similar changes. The enhanced intraduodenal glutamine levels of the HIV + subjects

Table Free amino-acids (mmol/kg dry weight) in biopsies of the duodenal mucosa, which are significantly different between HIV + patients and normals.

	Normals (n = 11)		HIV + patients (n = 6)			
AA	Means	(SD)	Means	(SD)	Median	p
THR	1.17	(0.12)	1.98	(0.69)	1.9	**
SER	2.20	(0.31)	3.60	(1.37)	3.6	**
GLU	17.03	(1.56)	24.13	(5.74)	22.3	***
GLN	2.61	(0.73)	5.65	(3.69)	4.0	**
VAL	1.65	(0.29)	2.20	(0.56)	2.3	***
ORN	0.37	(0.12)	1.38	(0.78)	1.0	***
Total	61.90	(5.43)	73.70	(19.5)	66.7	

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lead to the assumption that the intracellular degradation of glutamine might be disturbed in these persons. Whether these changes can also be induced by the methotrexate-induced enterocolitis [1] is now under investigation. Our data do not support the hypothesis of an intramucosal GLN-deficit in immunodeficient patients with opportunistic infections.

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The Effects of Sepsis on Intestinal and Pulmonary Glutamine Metabolism

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Although a variety of animal studies have demonstrated that interorgan glutamine metabolism is markedly altered during critical illness, the effects of sepsis need further elucidation. In addition, few studies have examined glutamine metabolism by specific organs in patients, due in large part to the inaccessibility of the visceral organs. We have recently defined a new and important role for the lung in glutamine metabolism. In addition, we have quantitated glutamine extraction by the human gastrointestinal tract in healthy and septic patients.

The flux of glutamine across the lung was determined in three groups of surgical patients with indwelling pulmonary artery catheters: (a) pre-operative controls ($n=14$), (b) post-operative elective general surgical patients (POD 1-GS, $n=10$), and (c) hyperdynamic septic surgical patients ($n=17$) [1]. In hyperdynamic septic patients, total pulmonary blood flow (cardiac output) increased by 73% above control levels to 111 ± 7 ml/kg BW/min ($p<0.001$). In controls, the lung was an organ of slight glutamine release and this exchange rate did not change significantly in POD 1-GS patients undergoing abdominal operation. In the septic group, glutamine releases by the lung increased markedly from a control value of 0.80 ± 0.99 mm/kg/min to 6.80 ± 1.32 ($p<0.01$). This accelerated release rate was secondary to both increased pulmonary blood flow and increased total pulmonary artery-systemic arterial concentration difference. The lungs appear to play an active role in the processing of glutamine and may be a key regulator of interorgan nitrogen flux following infection and other critical illnesses.

We studied intestinal glutamine extraction in 6 healthy surgical patients (controls) and 5 septic patients (4 perforated viscus, 1 perineal sepsis) who underwent laparotomy for their primary disease [2]. Arterial and portal vein samples were obtained in duplicate. Samples were analysed for PO_2 and glutamine. Glutamine and oxygen extraction by the gut were calculated. In controlled patients, the arterial glutamine was 611 ± 52 umol/l compared to 546 ± 39 in the septic patients ($p=$NS). However, gut glutamine extraction fell significantly with severe infection from $12 \pm 2\%$ in controls to $3 \pm 1\%$ in septic patients ($p<0.05$). Likewise, oxygen extraction was reduced by 50% in septic man from 11% to 6%.

In order to gain further insight into the effects of sepsis on intestinal glutamine metabolism, endotoxin (10 mg/kg IP $n=24$ or saline) controls ($n=20$) was administered to adult rats 15 h prior to cannulation of the