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THE EFFECT OF INTRAVENOUS XYLITOL ON THE CONCENTRATION OF ADENINE NUCLEOTIDES IN HUMAN LIVER

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Abstract—Xylitol was infused intravenously during a 30-min period to patients undergoing uncomplicated cholecystectomy. A 50-g dose caused a decrease in the hepatic ATP concentration from 2.75 to 0.25 μmole/g liver and in the concentration of inorganic phosphate from 3.6 to 1 μmole/g. The hepatic content of adenine nucleotides was reduced to 30 per cent of the control value. The concentration of L-glycerol 3-phosphate increased to 5 to 10 μmole/g, and glucose, lactate and ketone bodies remained unchanged.

Xylitol has been increasingly used as an intravenous nutrient in recent years [1]. The normal clinical use is accompanied by an increase in serum bilirubin, in the activity of hepatic enzymes in serum [2] and by a definite increase in the concentration of uric acid in serum [3]. In rare cases a lethal precipitation of calcium oxalate in the renal tissue has been reported [4].

Now xylitol is introduced as a sweetener because it has a low cariogenic effect [5], and therefore it becomes more important to know about its metabolic effects in humans. One major question remains to be answered: does xylitol show as detrimental effects on the human liver adenine nucleotide system as it does in rat liver [6]? The concentration of uric acid increases more after xylitol than after an equivalent dose of fructose [3], and as the degradation of adenine nucleotides proceeds via AMP to IMP with uric acid as the final product in human liver this suggests xylitol to be more active than fructose in lowering the hepatic adenine nucleotide concentration in humans.

Therefore it was considered relevant to measure the metabolic effect of xylitol on human liver.

MATERIALS AND METHODS

Biopsies were performed surgically in patients who underwent cholecystectomy for uncomplicated cholelithiasis. Informed consent was obtained prior to the operation. The biopsies were immediately freeze-clamped using aluminium tongs precooled in liquid nitrogen. The biopsies were about 0.5 g weight and were precipitated in 3 ml perchloric acid (6%) after cutting by a Sorvall Omnimixer. The precipitate was centrifuged and the supernatant was neutralized with 6 N KOH.

Fifteen min after the initiation of anestesia with halothane and N_2O/O_2, a continuous infusion of xylitol 10% (Xylit, Pfremmer, Erlangen, Germany) was started. Using an Infusomat (Braun Melsungen, Germany) 25 or 50 g xylitol were infused at a constant rate during a 30 min period. Biopsy was performed at the end of the xylitol infusion. Control values were obtained from three patients to whom no xylitol was given.

Pyruvate and acetoacetate were determined enzymatically [7] the same day as the biopsy was taken. Adenine nucleotides were determined the next day [8, 9] and glycerol and glycerol 3-phosphate, [10] glucose [11], lactate [12], 3-hydroxybutyrate[13], and inorganic phosphate [14] were determined within 1 week.

RESULTS AND DISCUSSION

The results are given in Table 1. The control values for ATP in the biopsies are in the same range as found previously in humans [15], and in rat liver using the same technique [16]. Xylitol (50g/30 min) causes a severe and reproducible decrease in the ATP concentration to about 10 per cent of the normal value. The decrease seems to be dose-dependent since a dose of 25 g/30 min causes a decrease in the ATP concentration to 30 per cent of the control value. The concentration of ADP decreases also whereas the AMP concentration remains unchanged. The hepatic content of adenine nucleotides is reduced by 70 per cent by 50 g xylitol and by 60 per cent by 25 g. From the reduction in hepatic adenine nucleotide concentration a minimum production of 650 mg uric acid can be calculated assuming the liver weight to be 1500 g. This may well account for the observed increase of 30 mg/l in serum uric acid after a comparable dose of xylitol [3]. It is therefore likely that the increase in uric acid concentration after xylitol is due to an increased degradation of nucleotides in the liver.

The concentration of inorganic phosphate is also decreased in the liver after xylitol infusion (Table 1), and some inorganic phosphate is trapped in L-glycerol 3-phosphate which accumulates. The increase in ester-bound phosphate in L-glycerol 3-phosphate

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Table 1. Effect of intravenous xylitol on some metabolites in human liver

	Xylitol given i.v. over 30 min (g)				
	0	25		50	
	(n = 3)	A	B	A	B
ATP	2.74 ± 0.46	1.06	0.73	0.30	0.21
ADP	0.65 ± 0.03	0.36	0.34	0.58	0.52
AMP	0.18 ± 0.08	0.03	0.15	0.22	0.21
Sum of adeninenucleotides	3.57 ± 0.53	1.45	1.22	1.10	0.94
Inorganic phosphate	3.46 ± 0.26	1.32	1.07	0.95	0.78
Decrease in Pi		7.91	9.10	9.93	10.50
L-glycerol 3-phosphate	0.76 ± 0.44	4.14	4.07	4.36	8.91
Increase in Pi		3.42	3.35	3.63	8.15
Glycerol	0.55 ± 0.07	0.85	0.98	0.41	0.61
Glucose	7.05* ± 1.41	3.05	5.43	5.91	4.76
Lactate	5.92* ± 1.20	3.15	3.80	2.64	4.16
Pyruvate	0.09 ± 0.05	0.11	0.04	—	—
3-hydroxybutyrate	2.28 ± 0.62	1.21	1.66	2.21	1.78
Acetoacetate	—	0.09	0.07	0.05	—

The xylitol was given over 30 min at a constant rate and the period was finished by a biopsy. A and B denotes individual patients in each group. The control values are given ± S.E.M. Decrease in Pi means the sum of Pi lost in adenine nucleotides plus that from inorganic phosphate. The increase in Pi means Pi accumulated during the perfusion period in L-glycerol 3-phosphate. The values are μmole/g liver wet wt. * One glucose concentration was 9.9 μmole/g and the lactate concentration was 7.4 in the same patient, who had a blood loss of 2 l in the initial period of the operation.

accounts for 40 to 50 per cent of the phosphate which has disappeared by the decrease in adenine nucleotides and inorganic phosphate. It is striking that the concentration of inorganic phosphate attains such low values during steady-state xylitol infusion, since the decrease in inorganic phosphate after fructose administration is restored within few minutes by uptake of inorganic phosphate from the medium[17]. In rat liver perfused with xylitol [6], or glycerol [18], accumulation of a comparable amount of L-glycerol 3-phosphate is accompanied by a decrease in the concentration of ATP to only half the normal value, and the ATP concentration in human liver following infusion of 50 g fructose over 30 min was 1 μmole/g, i.e. four times the value after 50 g xylitol [15]. Thus human liver seems to be especially sensitive to the effects of xylitol on the adenine nucleotide system.

The mechanism by which the liver is depleted of adenine nucleotides is not fully elucidated. Inorganic phosphate and ATP act as inhibitors of the AMP degrading enzymes, AMP deaminase and 5-nucleotidase [19, 20] respectively, and a decreased inhibitor concentration has therefore been thought to be responsible for the increased rate of AMP degradation [21, 22]. The very low concentrations of ATP and inorganic phosphate in human liver metabolizing xylitol would favour the degradation of AMP to uric acid.

The changes in adenine nucleotides and inorganic phosphate must be expected to affect a long series of regulatory processes in the liver. The concentration ratio between ATP and ADP is reduced from 4.2 in the control biopsies to 2.5 and 0.5 with increasing xylitol dose. Therefore many processes of biosynthesis must be expected to be decreased. The activity of the adenyl cyclase must be expected to be decreased since the enzyme is sensitive to changes in the ATP concentration in the range about 1 mM [23]. The resulting decreased sensitivity to glucagon [24] may explain that xylitol infusion is not accompanied by any increase in blood glucose [3] whereas some glycogen accumulation has been found [25]. In the biopsies shown in Table 1 there was no change in the glucose concentration after xylitol.

The cytosolic free NADH/NAD concentration ratio expressed as the lactate to pyruvate concentration ratio increases during xylitol metabolism in the liver [6, 26]. This would tend to increase the lactate formation from pyruvate, but during xylitol metabolism in humans the lactate concentration in the blood remains unchanged [3], as it does in the liver biopsies (Table 1). The normal large lactate production in livers metabolizing fructose is also inhibited when the cytosolic NAD redox state is made more reduced by addition of ethanol. In this case the flux of carbon from the triose phosphate level to lactate is reduced [27], most likely because of the effect of an increased NADH/NAD on the combined glyceraldehyde 3-phosphate dehydrogenase–phosphoglycerate kinase reaction.

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