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Nicotinamide Counteracts Alcohol-Induced Impairment of Hepatic Protein Metabolism in Humans[1,2]

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ABSTRACT   We have recently shown that a large amount of wine (750 mL, ~70 g of alcohol) markedly impairs postprandial hepatic protein metabolism in healthy subjects. This is probably due to the shift in the intracellular redox state (increased $NADH/NAD^+$) induced by ethanol oxidation. If this hypothesis is true, the administration of nicotinamide (NAD^+ precursor) should provide NAD^+ in excess and thus correct the $NADH/NAD^+$ abnormalities and prevent the ethanol hepatotoxicity. Whole-body protein metabolism and the fractional secretory rates of hepatic (albumin, fibrinogen) and extra-hepatic (immunoglobulin G, IgG) plasma proteins were measured in the basal postabsorptive and in the absorptive states in 15 healthy subjects, that had been assigned to three groups matched for age and body mass index. During the absorptive state (intragastric meal), the three groups received water (control), 750 mL of wine, or 750 mL of wine + 1.25 g of nicotinamide, respectively. The redox state was estimated by determining the plasma lactate/pyruvate ratio. Compared with the basal state, wine alone increased the lactate/pyruvate ratio twofold and depressed the fractional secretory rates of albumin and fibrinogen ($P < 0.01$ vs. control and nicotinamide); nicotinamide reduced the effects of wine on the lactate/pyruvate ratio ($P < 0.02$ vs. wine alone) and prevented the reduction of albumin and fibrinogen secretory rates ($P > 0.05$ vs. control). These results indicate that nicotinamide counteracts the acute hepatotoxic effects of ethanol by ameliorating the redox state.   J. Nutr. 127: 2199–2204, 1997.

KEY WORDS: • *leucine kinetics* • *albumin synthesis* • *fibrinogen synthesis* • *humans* • *liver cirrhosis*

We have recently shown that the intake of 750 mL of wine (~70 g of ethanol) during meal absorption in normal subjects inhibits the fractional secretory rates of the two important hepatic proteins albumin and fibrinogen (De Feo et al. 1995). Ethanol appears to have acute and relatively specific effects on hepatic protein synthesis because fractional secretory rates of immunoglobulin G (IgG)[4] and leucine estimates of whole-body protein synthesis were unaffected by alcohol ingestion (De Feo et al. 1995). It is likely that the repeated intake of large amounts of alcohol contributes to the pathogenesis of the complications of chronic alcoholism such as liver cirrhosis and muscle myopathy by impairing the metabolism of secretory liver proteins. In fact, experiments in animals demonstrated that the impairment in hepatic protein metabolism plays a key role in the development of alcoholic liver injury (French 1989, Lieber 1980). Furthermore, studies in humans suggested that the postprandial inhibition of albumin secretion might induce muscle wasting also in the absence of poor protein intake (Baumgartner et al. 1996, De Feo et al. 1992).

Although the role of albumin in whole-body amino acid and protein homeostasis is not well defined, it is known that albumin synthesis is stimulated by insulin (De Feo et al. 1993, Volpi et al. 1996) and/or meal ingestion of amino acids (Volpi et al. 1996) and that it is catabolized by nearly every tissue in the body (Yedgar et al. 1983). Approximately 30% of the increase in whole-body protein synthesis observed during meal absorption can be accounted for by the increase in albumin synthesis (De Feo et al. 1992). One potential nutritional role of albumin is as a temporary storage pool of amino acids, protecting some fraction of ingested amino acids from irreversible oxidation and thus ensuring their delivery to peripheral tissues for utilization in protein synthesis days after their intake. This hypothesis is consistent with studies in dogs, demonstrating that hepatic secreted plasma proteins may serve as an important source of amino acids for protein synthesis in muscle and other peripheral tissues (Elwyn 1970, Elwyn et al. 1968), and in elderly humans, in whom serum albumin concentration significantly associates with muscle mass (Baumgartner et al. 1996). Thus any factor(s) that might interfere with the synthesis of albumin during meal absorption (i.e., ethanol) could have significant effect on whole-body and particularly muscle protein homeostasis if such a process was extended over time.

The mechanism by which alcohol acutely impairs liver pro-

TABLE 1

Leucine infusion rates, [14]CO[2] excretion rates, plasma leucine and α-ketoisocaproicacid (KIC) specific activities and whole-body leucine kinetics in normal humans in the postabsorptive period (basal) and during the intragastric (ig) administration of a mixed meal combined with the ingestion of water (control) or wine with (NA) or without (W) the administration of nicotinamide[1,2]

	Control group		W group		NA group	
	Basal	Meal	Basal	Meal	Basal	Meal
	dpm/(kg · min)					
Intravenous [1-^{14}C]leucine infusion rate	8180 ± 430		7610 ± 240		7870 ± 670	
[14]CO[2] excretion rate	616 ± 157	1380 ± 135	839 ± 137	1184 ± 109	578 ± 120	897 ± 128
	dpm/nmol					
Plasma leucine specific activity	5.43 ± 0.96	4.49 ± 0.84	4.93 ± 0.84	4.06 ± 0.53	6.25 ± 0.81	4.71 ± 0.72
Plasma KIC specific activity	3.39 ± 0.28	2.84 ± 0.35	3.21 ± 0.56	2.68 ± 0.23	3.25 ± 0.19	2.97 ± 0.27
	μmol/(kg · min)					
Total leucine Ra[3]	2.41 ± 0.08	2.89 ± 0.08	2.41 ± 0.14	2.85 ± 0.09	2.41 ± 0.09	2.67 ± 0.12
Ig leucine infusion rate		1.47 ± 0.17		1.35 ± 0.03		1.22 ± 0.16
Endogenous leucine Ra	2.41 ± 0.08	2.02 ± 0.12*	2.41 ± 0.14	1.60 ± 0.19*	2.41 ± 0.09	2.05 ± 0.12*
Leucine oxidation rate	0.26 ± 0.04	0.60 ± 0.03*	0.39 ± 0.07	0.54 ± 0.05*‡	0.26 ± 0.06	0.39 ± 0.07*‡
Nonoxidative leucine disposal	2.15 ± 0.09	2.29 ± 0.10*	2.02 ± 0.08	2.31 ± 0.06*	2.15 ± 0.09	2.29 ± 0.06*
Net leucine balance	−0.26 ± 0.04	0.88 ± 0.20*	−0.39 ± 0.07	0.80 ± 0.07*	−0.26 ± 0.06	0.84 ± 0.16*

[1] Values are means ± SEM, $n = 5$. * $P < 0.01$ vs. basal; ‡ $P < 0.01$ vs. control. No differences were found between the W and NA groups.
[2] 1 Bq = 60 dpm.
[3] Ra, rate of appearance.

tein metabolism has been investigated in vitro. In cultured rat hepatocytes, ethanol oxidation leads to the consumption of NAD^+, which is reduced to NADH. The subsequent shift in the redox equilibrium toward the reduced state (increased $NADH/NAD^+$ ratio) is the most likely cause of the impairment in hepatic intermediate metabolism (French 1989, Lieber 1980). In fact, the administration of hydrogen ion acceptors such as methylene blue or high doses of hydrogen ion shuttles such as aspartate, that are able to reoxidize NADH, prevents ethanol inhibition of protein synthesis (Baraona et al. 1980). However these compounds are not safe for use in humans. Recent studies have shown that nicotinamide administration increases the intracellular NAD^+ pool (Pociot et al. 1993) because nicotinamide is the direct precursor for NAD^+ synthesis (Mayes 1990).

The present study was undertaken to test the hypothesis that administration of the NAD^+ precursor, nicotinamide, by increasing the intracellular availability of NAD^+, can reduce or reverse the inhibitory effect of acute ethanol ingestion on liver protein metabolism, specifically on the meal-induced increase in albumin synthesis.

SUBJECTS AND METHODS

Protocol. After receiving Institutional Review Board approval, informed written consent was obtained from 15 healthy volunteers (5 women, 10 men), with normal physical examinations and routine blood analysis, and with no serological evidence of viral hepatitis. All subjects reported occasional consumption of moderate amounts of alcoholic beverages (ethanol < 100 g/wk). The subjects were divided into three groups and given water (control, $n = 5$), or 750 mL of wine (W, $n = 5$), or 750 mL of wine plus nicotinamide (NA, $n = 5$) with a mixed meal. Groups were matched for age (control 24 ± 1, W 25 ± 1, NA 23 ± 1 y) and body mass index (control 21 ± 1, W 22 ± 1, NA 23 ± 1 kg/m^{2}).

All subjects were studied 3 d after consuming a weight-mainte-

nance diet of 146 kJ/(kg · d) containing 55, 30 and 15% carbohydrate, fat and protein, respectively; no alcoholic beverages were permitted. After overnight fasting, the volunteers were admitted to the Clinical Research Unit of the Dipartimento di Medicina Interna e Scienze Endocrine e Metaboliche of the University of Perugia, Italy, at ~0730 h. At ~0800 h, a 23-gauge catheter was placed in an antecubital vein for the infusion (Harvard syringe pump, Harvard Apparatus, Ealing, South Natick, MA) of [1-^{14}C]leucine (specific activity 2 MBq/ mmol, Amersham International, Buckinghamshire, UK) and saline (0.5 mL/min, Vial Médical pump, Grenoble, France). A contralateral hand vein was cannulated in a retrograde fashion with a 20-gauge butterfly needle; the hand was maintained at 65°C in a thermoregulated Plexiglas box to permit intermittent sampling of arterialized-venous blood (McGuire et al. 1976). An 8F size nasogastric feeding tube was inserted for intragastric (ig) meal infusion.

At ~0900 h (time, 0 min), a primed-constant intravenous infusion of L-[1-^{14}C]leucine [prime, 333 kBq/min (9 μCi); infusion rate, 11.1 kBq/min (0.3 μCi/min)], was started and continued for 8 h. At time 240 min, after blood and breath sampling, the ig infusion of a liquid mixed meal was started (1.75 mL/min) and continued throughout the study (Vial Médical pump). The meal provided 2642 kJ (17% from amino acids, 33% from lipids and 50% from carbohydrates). It was prepared by mixing a complete formula of nonessential and essential amino acids (Isopuramin Plus 10%, Bieffe Medical, Modena, Italy; ig unlabeled leucine infusion rate reported in **Table 1**) with 84 g of glucose and a mixed oil solution (Lipofundin S, B. Braun, Melsungen, Germany). Either 150 mL of natural spring water (Santa Chiara, Motette srl, Scheggia, Italy) (control group), or 150 mL of white wine (12% v/v ethanol content, Pergoleto Lungarotti, Cantine Lungarotti srl, Torgiano, Italy) (W and NA groups) were given to the volunteers at the beginning of the meal infusion. Then, 50 mL water (control group) or 50 mL wine (W and NA groups) was given every 15 min (from 255 to 420 min) for a total of 750 mL water to the control group, and 750 mL wine to the W and NA groups. At 240 min, the subjects of the NA group were given two tablets of nicotinamide (250 mg per tablet, IDI, Pomezia, Italy), and three other tablets were dissolved into their meal (~1.78 g/L of meal) and infused, for a total amount of 1.25 g nicotinamide.
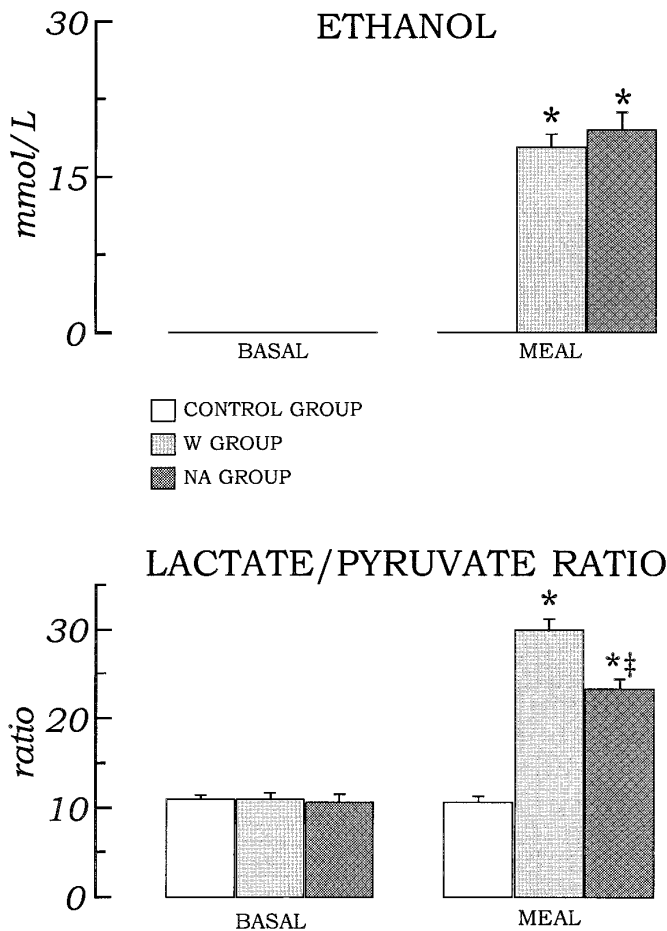
FIGURE 1 Plasma concentrations of ethanol and the lactate/pyruvate ratio in normal humans during the overnight postabsorptive state (BASAL), and during the absorption of a meal (MEAL) plus either water (CONTROL) or 750 mL of wine with (NA) or without (W) nicotinamide. Values are means $\pm$ SEM, $n = 5$. *$P < 0.0001$ vs. CONTROL; ‡$P < 0.02$ vs. W.

Blood (16 mL) and breath samples were collected at -15, 0, 180, 200, 220, 240, 420, 440, 460 and 480 min to measure the plasma concentrations of glucose, lactate, pyruvate, insulin, isoleucine, leucine, α-ketoisocaproic acid (KIC), albumin, fibrinogen and IgG, the plasma specific activity of leucine and KIC, the rates of expired total CO_2, total $^{14}CO_2$ and CO_2 specific activity, and the specific activity of leucine derived from albumin, fibrinogen and IgG hydrolysis. Plasma ethanol concentrations (1 mL blood) were measured every 60 min from 240 to 480 min.

Analytical methods. The plasma concentrations of glucose (Beckman glucose analyzer, Palo Alto, CA), insulin (Herbert et al. 1965), albumin (Doumas et al. 1971), fibrinogen (Jacobsoon 1955), IgG (Whicher et al. 1984), ethanol (Lundquist 1957), lactate and pyruvate (Olsen 1971) were determined as previously described. The plasma concentrations of isoleucine, leucine, and KIC, the leucine concentration into the infused mixed meal, the dpm (disintegrations per minute) of the leucine infusate, the specific activity of plasma leucine and KIC (Horber et al. 1989), the specific activity of leucine derived from hydrolyzed albumin, fibrinogen and IgG (De Feo et al. 1995), the specific activity of expired CO_2 and the ^{14}C radioactivity in KIC, leucine and CO_2 (Horber et al. 1989) were determined as previously described.

Calculations. The rates of radiolabeled leucine administration were calculated multiplying the disintegrations per minute (dpm) per milliliter of infusate, by the infusion rate (mL/min).

The estimates of whole-body leucine kinetics were determined on the data obtained during the last hour of each study period (postabsorptive state: 180–240 min; absorptive state: 420–480 min) at the isotopic and metabolic steady state, using the four-compartment model (Schwenk et al. 1985). The rate of total leucine appearance [Total Ra, μmol/(kg·min)] was calculated using the following formula:

$$\text{Total Ra} = \frac{i}{\text{SA}_{KIC}}$$

where i is the labeled leucine infusion rate [dpm/(kg·min)] and SA_{KIC} is the plasma KIC specific activity (dpm/μmol). During meal administration, the rate of endogenous leucine appearance [Endogenous Ra, μmol/(kg·min)], an index of whole-body proteolysis, was calculated as follows:

$$\text{Endogenous Ra} = \text{Total Ra} - D_{Leu}$$

where D_{Leu} is the ig leucine infusion rate. The rate of leucine oxidation [Ox, μmol/(kg·min)] was calculated using the precursor-product model:

$$\text{Ox} = \frac{\Phi CO_2}{\text{SA}_{KIC}} \cdot \frac{1}{\alpha}$$

where ΦCO_2 is the $^{14}CO_2$ excretion rate [dpm/(kg·min)] and α is the correction factor for the CO_2 recovery, assuming values of 0.70 and 0.82 in the postabsorptive and absorptive states (Hoerr et al. 1989), respectively. The rate of nonoxidative leucine disposal [NOLD, μmol/(kg·min)], index of whole-body protein synthesis and net leucine balance [Balance, μmol/(kg·min)] were estimated as follows:

$$\text{NOLD} = \text{Total Ra} - \text{Ox}$$

$$\text{Balance} = \text{NOLD} - \text{Endogenous Ra}$$

The fractional secretory rates (FSR, %/h) of plasma proteins were calculated using the precursor-product model:

$$\text{FSR} = \frac{\Delta \text{SA}_{Leu\ protein}/\Delta t}{\text{SA}_{KIC\ plasma}} \cdot 100 \cdot 60$$

where $\Delta \text{SA}_{Leu\ protein}/\Delta t$ is the incorporation rate of labeled leucine into proteins from 180 to 240 min (postabsorptive state) and from 420 to 480 min (absorptive state), and $\text{SA}_{KIC\ plasma}$ is the mean plasma KIC specific activity during the same time periods. The use of plasma KIC specific activity as precursor pool specific activity for hepatic protein synthesis in the postabsorptive and the absorptive states has been recently validated (De Feo et al. 1995, Volpi et al. 1996).

Statistical analysis. Statistical analysis was performed with the SAS/STAT, Version 6.10 (SAS Institute, Cary, NC). The effects of treatments on response variables in the postabsorptive (180–240 min) and absorptive (420–480 min) states were analyzed using ANOVA for repeated measures (Winer 1972). Specific contrast matrices (planned comparisons method) were constructed to evaluate differences among group means. Data are expressed as means $\pm$ SEM. Linearity of label incorporation into plasma proteins was tested according to the method suggested by Snedecor and Cochran (1980).

RESULTS

Plasma concentrations of glucose, insulin, ethanol and lactate/pyruvate ratio. Plasma concentrations of glucose and insulin increased during meal absorption ($P < 0.001$ vs. basal) without differences among the three groups (data not shown).

Plasma ethanol concentrations were undetectable at 240 min in the three groups. In the second study period (absorptive state), they remained undetectable in the control group until the end of the study, whereas they increased significantly in the W and NA groups without differences between the two groups (**Fig. 1**).

The plasma lactate/pyruvate ratio (mol/mol) did not differ among the three groups in the postabsorptive state and did not change in the control group during meal absorption, whereas it increased by~200% in the W group and only ~100% in the

TABLE 2

Albumin, fibrinogen and immunoglobulin G (IgG) tracer incorporation rates ($\Delta SA/\Delta t$) and fractional secretory rates (FSR) in normal humans in the postabsorptive period (basal) and during the intragastric (ig) administration of a mixed meal combined with the ingestion of either water (control) or wine with (NA) or without (W) the administration of nicotinamide[1]

	Control group		W group		NA group	
	Basal	Meal	Basal	Meal	Basal	Meal
	dpm/(μmol · min)					
$\Delta SA/\Delta t$						
Albumin	0.190 ± 0.035	0.231 ± 0.055	0.184 ± 0.011	0.129 ± 0.016	0.143 ± 0.005	0.166 ± 0.012
Fibrinogen	0.567 ± 0.117	0.521 ± 0.117	0.550 ± 0.139	0.446 ± 0.115	0.507 ± 0.056	0.510 ± 0.056
IgG	0.105 ± 0.025	0.120 ± 0.016	0.084 ± 0.007	0.088 ± 0.011	0.092 ± 0.014	0.103 ± 0.019
	%/h					
FSR						
Albumin	0.335 ± 0.020	0.486 ± 0.038*	0.347 ± 0.015	0.288 ± 0.028*‡	0.265 ± 0.011	0.346 ± 0.040*
Fibrinogen	1.031 ± 0.100	1.199 ± 0.123	1.096 ± 0.096	0.978 ± 0.080†	0.931 ± 0.079	1.041 ± 0.099
IgG	0.184 ± 0.016	0.253 ± 0.012*	0.178 ± 0.016	0.228 ± 0.027*	0.168 ± 0.021	0.208 ± 0.027*

[1] Values are means ± SEM, $n = 5$. * $P < 0.01$ vs. basal; ‡ $P < 0.001$ vs. control and NA; † $P < 0.01$ vs. control and NA.

NA group, with a significant difference between these two groups (Fig. 1).

Whole-body leucine kinetics. Over the last hour of the postabsorptive and absorptive periods, the concentrations and the specific activities of plasma leucine and KIC, and expired CO_2 specific activity were at steady state (data not shown). In the postabsorptive state, whole-body leucine kinetics did not differ among the three groups (Table 1). Meal administration decreased endogenous leucine rate of appearance ($P < 0.0001$ vs. basal) and increased nonoxidative leucine disposal ($P < 0.01$ vs. basal) and leucine net balance ($P < 0.0001$ vs. basal), without differences among the three groups. Leucine oxidation rate increased with meal absorption in the three groups ($P < 0.0001$ vs. basal), but wine intake partially blunted

this increment in the W ($P = 0.0099$ vs. control) and NA groups ($P = 0.0044$ vs. control) (Table 1).

Plasma protein concentrations and fractional secretory rates. The plasma concentrations of albumin, fibrinogen and IgG were not different among the three groups and did not change during meal intake (data not shown).

The specific activity of leucine derived from the hydrolysis of the three plasma proteins increased linearly during the last hour of each study period (data not shown).

Meal administration (**Table 2, Fig. 2**) changed albumin fractional secretory rate ($P < 0.01$ vs. basal) with a significant time by group interaction ($P < 0.001$). Albumin fractional secretory rate increased similarly in the control and NA groups to rates that did not differ from one another, whereas it de-
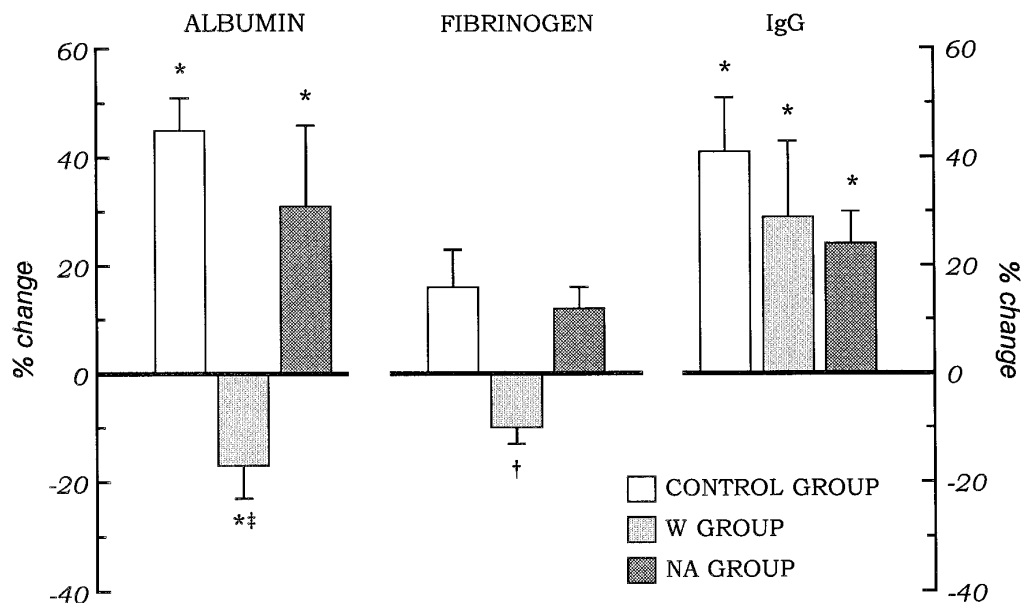

FIGURE 2 Percentage change from the postabsorptive values of the fractional secretory rates of plasma hepatic (albumin and fibrinogen) and extrahepatic [immunoglobulin G (IgG)] proteins in three groups of healthy subjects during the absorption of a mixed meal plus either water (CONTROL) or 750 mL of wine with (NA) or without (W) nicotinamide. Values are means ± SEM, $n = 5$. *$P < 0.01$ vs. the postabsorptive state; ‡$P < 0.001$ vs. CONTROL and NA; †$P < 0.01$ vs. CONTROL and NA.

creased in the W group ($P < 0.001$ vs. control and NA). Fibrogen fractional secretory rate was unaffected by meal absorption in the control and NA groups, whereas it decreased in the W group ($P < 0.01$ vs. control and NA).

IgG fractional secretory rate increased during meal absorption ($P < 0.001$ vs. basal), without differences among the three groups (Table 2, Fig. 2).

DISCUSSION

Administration of the NAD^+ precursor nicotinamide counteracted the profound inhibitory effect of acute ethanol ingestion on postprandial albumin and fibrinogen synthesis and/or secretion in healthy humans. Specifically, nicotinamide restored the physiologic meal-induced increase in albumin fractional secretory rate, and maintained fibrinogen fractional secretory rate, which is not influenced by meal absorption (De Feo et al. 1995, Volpi et al. 1996 and control group of the present study), within the normal values. The effect of nicotinamide is restricted to the liver, because IgG fractional secretory rate and whole-body protein metabolism parameters were not different in the two groups given wine either with or without nicotinamide. In particular, the ethanol-dependent reduction in leucine oxidation rate, which is probably due to a substrate competition mechanism (extensively discussed in De Feo et al. 1995), was similar in the two groups given ethanol either with or without nicotinamide.

The lactate/pyruvate ratio is a good index of the intrahepatic redox state, because any variations in the $NADH/NAD^+$ ratio are reflected by an according shift in the lactate:pyruvate equilibrium (i.e., an increase in NADH will increase the reduction of pyruvate to lactate) (French 1989, Lieber 1980). The increase in lactate/pyruvate ratio with ethanol ingestion and the significant reduction of these changes with the simultaneous administration of nicotinamide provide evidence that the ethanol-induced decrease in albumin and fibrinogen synthesis is directly or indirectly related to a change in the redox state of the liver. In vitro studies suggest that the synthesis of liver proteins is reduced as a result of an ethanol-induced depletion of ATP (Lieber 1980, Masson et al. 1993). The oxidation of both ethanol and its primary metabolite, acetaldehyde, increases the $NADH/NAD^+$ ratio, which secondarily decreases the activity of key enzymes on ATP-producing pathways such as glycolysis (Berry et al. 1994), β-oxidation (French 1989) and the tricarboxylic acid cycle (Lieber 1980). This relative depletion of ATP could be compounded by the shunting of glycerol-3-phosphate to triglyceride synthesis as a result of increased acetyl-CoA availability from ethanol oxidation (French 1989).

A second potential mechanism for the effect of nicotinamide is at the level of hepatic protein secretion (Sorrell et al. 1983). In cultured hepatocytes, acetaldehyde generated from ethanol oxidation by reacting with tubulin impairs tubulin polymerization and inhibits the secretory process (Tuma et al. 1987). We measured the FSR of secretory proteins in the plasma space; therefore any processes that inhibited secretion alone would prevent the entry of labeled protein into the sampling space and thus reduce its FSR. Because NAD^+ is the coenzyme for aldehyde dehydrogenase, nicotinamide administration would accelerate acetaldehyde oxidation by increasing the intracellular NAD^+ availability and thus maintain the secretory process of newly synthesized hepatic proteins. Although we cannot exclude this mechanism as a contributing factor, it is less attractive because of the very high concentrations of ethanol and acetaldehyde required in both in vivo and in vitro animal studies to demonstrate an effect on tubulin

polymerization. Additional studies will be required to specifically address this issue.

Finally, on the basis of in vitro data, it is possible to exclude a direct effect of nicotinamide on liver protein synthesis and/or secretion, because the addition of the vitamin to liver cell cultures did not change either the secretion rate or the intracellular mRNA levels of albumin and α_1-acid glycoprotein (Barraud et al. 1995).

We would suggest that the nicotinamide administration during ethanol ingestion maintained the intracellular NAD^+ concentration, reducing the increase in the $NADH/NAD^+$ (and in the lactate/pyruvate) ratio, and thus maintained the production of ATP, albumin and fibrinogen.

In any case, the main result of this study is the nicotinamide-induced reversal of the alterations due to acute ethanol metabolism on postprandial liver protein secretion. Such an observation may have practical importance and application. Chronic alcohol abusers are reported to have an inverse correlation between alcohol intake and plasma fibrinogen (Krobot et al. 1992) and albumin concentrations (Lindholm et al. 1991) and are at increased risk for alcohol-induced myopathy (Preedy and Peters 1990). These complications could be explained if ethanol ingestion on a habitual basis chronically inhibits albumin and fibrinogen synthesis and if albumin is an important nutrient pool for many essential amino acids. Our results suggest that these alterations might be prevented with the administration of nicotinamide. In addition, it is possible that the impairment in hepatic protein metabolism may play a key role in the development of alcoholic liver injury (Lieber 1980). Were this the case, could it also be prevented with the administration of nicotinamide? The health care implications and costs in health care dollars and loss of productivity as a result of ethanol-induced hepatic damage are profound (Lieber 1995). The low cost of nicotinamide and the absence of side effects at doses twice as high as those used in the present study might make it a very cost-effective intervention strategy with a wide therapeutic safety margin in the prevention of liver disease in alcoholics who refuse to abstain from ethanol ingestion.

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