fetoprotein, albumin and cell surface–exposed components. Cancer Res 1988;48:4909-4918.
2. Gall JAM. Morphological and immunohistochemical assessment of intrahepatic bile duct development in the rat. J Gastroenterol Hepatol 1989;4:241-250.
3. Ruebner BH, Blankenberg TA, Burrows DA, Soohoo W, Lund JK. Development and transformation of the human hepatocytic-ductal plate [Abstract]. Lab Invest 1989;60:7P.
4. Shah K, Gerber MA. Development of intrahepatic bile ducts in humans: immunohistochemical study using monoclonal cytokeratin antibodies. Arch Pathol Lab Med 1989;113:1135-1138.
5. Van Eyken P, Sciot R, Callea F, Van der Steen K, Moerman P, Desmet VJ. The development of the intrahepatic bile ducts in man: a keratin-immunohistochemical study. HEPATOLOGY 1988;8:1586-1595.
6. Van Eyken P, Sciot R, Desmet V. Intrahepatic bile duct development in the rat: a cytokeratin-immunohistochemical study. Lab Invest 1988;59:52-59.
7. Carthew P, Edwards RE, Hill RJ, Evans JG. Cytokeratin expression in cells of the rodent bile duct developing under normal and pathological conditions. Br J Exp Pathol 1989;70:717-725.
8. Osborn M, Van Lessen G, Weber K, Klöppel G, Altmannsberger M. Methods in laboratory investigation: differential diagnosis of gastrointestinal carcinomas by using monoclonal antibodies specific for individual keratin polypeptides. Lab Invest 1986;55:497-504.
9. Van Eyken P, Sciot R, Callea F, Ramaekers F, Schaart G, Desmet VJ. A cytokeratin-immunohistochemical study of hepatoblastoma. Hum Pathol 1990;21:302-308.
10. Desmet VJ. Modulation of biliary epithelium. In: Reutter W, Popper H, Arias IM, Heinrich PC, Landmann L, eds. Modulation of liver cell expression. Lancaster: MTP Press, 1987;195-214.
11. Sell S, Dunsford HA. Evidence for the stem cell origin of hepatocellular carcinoma and cholangiocarcinoma. Am J Pathol 1989;134:1347-1363.

EFFECT OF LACTULOSE ON THE METABOLISM OF SHORT-CHAIN FATTY ACIDS

Mortensen PB, Holtug K, Bonnen H, Clausen MR. The degradation of amino acids, proteins, and blood to short-chain fatty acids in colon is prevented by lactulose. Gastroenterology 1990;98:353-360.

ABSTRACT

Short-chain (C_2-C_5) fatty acids account for 60%-70% of the anions in the colon. Acetate (C_2) is nontoxic in contrast to $C_{(3)4}$-C_5 fatty acids (propionate, butyrate, isobutyrate, valerate, and isovalerate), which induce coma in animals and may be important in the pathogenesis of hepatic coma in humans. An in-vitro fecal incubation system was used to map out short-chain fatty acid production in the presence of lactulose, amino acids, albumin, or blood. Albumin and blood increased production of all C_2-C_5 fatty acids. In contrast, lactulose was converted to acetate only and increased fecal acidity. The degradation of amino acids, albumin, and blood to short-chain fatty acids was completely inhibited by 10-25 mM lactulose. This was caused mainly by the acidifying effect of lactulose. pH-independent inhibition of blood and amino acid degradation to short-chain fatty acids required concentrations of lactulose exceeding 50-100 mM. Thus, the effect of lactulose in the treatment of hepatic coma may be related to its rapid fermentation into organic acids at rates exceeding colonic buffering capacity. This probably reduces formation of toxic fatty acids and ammonia from amino acids, polypeptides, and blood in the colon.

COMMENTS

The role of short-chain fatty acids (SCFA) in the pathogenesis of portalsystemic encephalopathy (PSE) has been suggested by numerous experimental studies (1). Increased levels of SCFA in plasma, primarily of five and six carbon fatty acids (i.e., valeric and hexanoic acids) and to a lesser degree, of butyric and octanoic acids have been documented in patients with hepatic coma (2). Presumably, these SCFA are produced in the bowel. Synergism between SCFA, ammonia and mercaptans has been implicated in the pathogenesis of PSE (1). Such a multifactorial etiology, indeed, is a logical explanation for this complex syndrome.

Nonstarch polysaccharides are fermented in the human colon by anaerobic bacteria. Hydrolysis of these polymers yields glucose, galactose, xylose, arabinose, fructose and uronic acid. During the process of fermentation a number of intermediates are formed including ethanol, methanol, formate, lactate and succinate, which are rarely found in human colon because they are rapidly metabolized to acetic, propionic and butyric acids. These acids are produced simultaneously with hydrogen, carbon dioxide and methane. Thus, SCFA give rise to the predominant anions in feces (3), and acetate is the predominant SCFA in the colon. Relative proportions of the three main SCFA are remarkably similar, with molar ratios of 59:23:17 of acetate, propionate and butyrate, respectively (4). Other SCFA such as isobutyrate are also present in small amounts. These SCFA originate primarily from the breakdown of proteins. Fecal SCFA concentrations and molar ratios remain relatively constant in man. Moreover, SCFA output in humans increases with increasing fecal volume, irrespective of the method of increasing fecal output (i.e., the addition of wheat bran, of nonabsorbable sugars, or of $MgSO_4$).

The work reported by Mortensen et al., under comment herein, describes further investigations of the metabolism of individual amino acids and their conversion to SCFA. These investigators suggest that the addition of lactulose increases the yield of acetate, which is the least toxic of the SCFA. The modification in the metabolic pathway of proteins and amino acids to form SCFA is particularly evident in the case of fecal incubation of blood in the presence of lactulose in which SCFA production is shifted almost completely to acetate. Fecal incubation with lactulose did not affect the production of butyrate and valerate, whereas the addition of albumin increased both ($p < 0.001$). Incubation with albumin did not apparently change the molar ratios of SCFA compared with control incubations but increased significantly the production of potentially toxic SCFA (i.e., butyrate and valerate).

The mechanisms of action of lactulose in the treatment of PSE are multiple. It is fascinating to see the wide spectrum of activities that this simple disaccharide can induce, including:

1. *Laxative effect*, which reduces the time for the production and absorption of ammonia and increases the nitrogen content of feces;

2. *Acidifying effect*, which reduces the absorption of ammonia and nitrogen;
3. *Utilization effect*, which increases the incorporation of ammonia-nitrogen into bacteria;
4. *Antiendotoxin effect*, which, although clinically speculative, has been demonstrated experimentally;
5. *Increased zinc absorption*, an effect that has been proved with lactose.

According to Mortensen et al. we may add to the list a sixth: *enhancement of acetate production*.

Most of the early studies focused attention on *in vivo* or *in vitro* pH reduction (5). Indeed, nonacidifying enemas have been used to treat acute PSE, but with less success than disaccharide enemas that acidify the feces (6). Apart from decreasing absorption of nonionized ammonia resulting from decreased intestinal pH, lactulose appears to promote the use of ammonia by colonic bacteria. The work of Mortensen et al. shows that lactulose is preferentially metabolized to acetate.

It seems clear that the degradation of amino acids, albumin and blood to toxic SCFA is largely inhibited by lactulose. Essentially we agree with the concept that this effect is nonspecific because the delivery of any carbohydrate to the colon, which does not receive significant amounts of sugar under physiological conditions, may exert similar effects. Hence, the alteration induced by lactulose may also be induced by lactose (7), lactitol (8), other sugars and even by nonstarch polysaccharides that undergo fermentation in the colon (9). It is interesting that the beneficial effects of dietary fiber may also be explained by the metabolism of polysaccharides in preference to amino acids. However, doubts exist about whether lactulose can convert all SCFA to acetate. Perhaps, this *in vitro* model may not be identical to the human colon.

The clinical applications of this very interesting article may include a reassessment of dietary prescriptions in patients with PSE. It seems reasonable that physicians can increase protein intake in such patients by adding a high carbohydrate supplement to the diet. Hepatologists should be about to start manipulating nitrogen and carbohydrate metabolism for the benefit of their encephalopathic patients (10).

MISAEL URIBE, M.D.
OCTAVIO CAMPOLLO, M.D., PH.D.
CHRISTIANE COTÉ, M.D.
Liver Unit
National Institute of Nutrition
1400 Mexico, D.F.

REFERENCES

1. Conn HO, Lieberthal MM. Pathogenesis of portal-systemic encephalopathy. In: The hepatic coma syndromes and lactulose, Baltimore: Williams & Wilkins, 1978:46-121.
2. Muto Y. Clinical study on the relationship of short chain fatty acids and hepatic encephalopathy. Jpn J Gastroenterol 1966;63:19-32.
3. Wrong O, Metcalfe-Gibson A, Morrison BI, Howard V. In vivo dialysis of feces as a method of stool analysis: techniques and results in normal subjects. Clin Sci 1965;28:357.
4. Cummings JH, Branch WJ. Fermentation and the production of short chain fatty acids in the human large intestine. In: Vahouny GV, Kritchvsky D, eds. Dietary fiber: basic and clinical aspects. New York: Plenum Press, 1986:131-149.
5. Meir KP. Progress in the treatment of portal systemic encephalopathy (PSE). J Hepatol 1987;5:355-361.
6. Uribe M, Campollo O, Vargas F, Ravelli GP, Mundo F, Zapata L. Acidifying enemas (lactitol and lactose) versus nonacidifying enemas (tap water) to treat portal systemic encephalopathy: a double blind randomized clinical trial. HEPATOLOGY 1987;7:639-643.
7. Uribe M, Marquez MA, Garcia-Ramos G. Treatment of chronic portal systemic encephalopathy with lactose in lactase deficient patients. Dig Dis Sci 1980;25:924-928.
8. Uribe M, Toledo H, Pérez F. Lactitol a second generation disaccharide for treatment of chronic portal systemic encephalopathy: a double blind randomized clinical trial. Dig Dis Sci 1987;32:1345-1353.
9. Pomare EW, Ranch WJ, Cummings JM. Carbohydrate fermentation in the human colon and its relation to acetate concentrations in venous blood. J Clin Invest 1985;74:1448-1454.
10. Uribe M. Nutrition, diet and hepatic encephalopathy. In: Layrargues GP, Butterworth RF, eds. Hepatic encephalopathy: pathophysiology and treatment. Clifton, NJ: Humana Press, 1989:529-548.

ALCOHOL CONTENT OF VARIOUS BEVERAGES: ALL BOOZE IS CREATED EQUAL

Frezza M, Di Padova C, Pozzato G, Terpin M, Baraona E, Lieber CS. High blood alcohol levels in women: the role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. N Engl J Med 1990;322:95-99.

ABSTRACT

After consuming comparable amounts of ethanol, women have higher blood ethanol concentrations than men, even with allowance for differences in size, and are more susceptible to alcoholic liver disease. Recently, we documented significant "first pass metabolism" of ethanol due to its oxidation by gastric tissue. We report a study of the possible contribution of this metabolism to the sex-related difference in blood alcohol concentrations in 20 men and 23 women. Six in each group were alcoholics.

The first pass metabolism was determined on the basis of the difference in areas under the curves of blood alcohol concentrations after intravenous and oral administration of ethanol (0.3 g per kilogram of body weight). Alcohol dehydrogenase activity was also measured in endoscopic gastric biopsies. In nonalcoholic subjects, the first pass metabolism and gastric alcohol dehydrogenase activity of the women were 23 and 59 percent, respectively, of those in the men, and there was a significant correlation (r_s = 0.659) between first pass metabolism and gastric mucosal alcohol dehydrogenase activity. In the alcoholic men, the first pass metabolism and gastric alcohol dehydrogenase activity were about half those in the nonalcoholic men; in the alcoholic women, the gastric mucosal alcohol dehydrogenase activity was even lower than in the alcoholic men, and first-pass metabolism was virtually abolished.

We conclude that the increased bioavailability of ethanol resulting from decreased gastric oxidation of ethanol may contribute to the enhanced vulnerability of women to acute and chronic complications of alcoholism.