Environmental Health Perspectives
Vol. 20, pp. 71–73, 1977

Ethanol and Development of Disease and Injury to the Alimentary Tract

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Effects of ethanol on the gastrointestinal tract are reviewed, and an overview of possible mechanisms of ethanol damage to the alimentary tract is presented. Ethanol toxicity most commonly results in malabsorption. Mechanisms contributing to ethanol-induced calcium malabsorption are considered in detail as a prototype for problems encountered in evaluating effects of toxicants on intestinal function. Effects at the local level in the intestine must be differentiated from systemic effects. The mechanism of suppression of calcium absorption by chronic ethanol ingestion differs from that produced by acute administration. Effects of acute administration appear to be due to local mucosal damage and are reversed in 18 hr. Such damage is not present with chronic administration, which affects only duodenal transport. Treatment with vitamin D and its metabolites does not reverse the inhibition of calcium transport. The overall findings suggest that ethanol inhibition of calcium transport is mediated at the intestinal level, probably affecting vitamin D independent mechanisms.

Introduction

One drug known to produce damage to the gastrointestinal tract is ethanol, probably the most commonly used/abused drug in both developed and developing countries. The mechanism of ethanol damage to the small intestine with resultant malabsorption of various nutrients may be very complex. Direct damage by the ingested toxicant is probably not the only mechanism involved. Indeed, ingested substances which themselves are not damaging may be metabolized to other substances in the gut by the intestinal mucosa or by bacteria residing in the intestine or by the liver and then re-excreted through the hepatobiliary system as products producing mucosal damage. Therefore, if a drug such as ethanol affects bowel motility, this in itself may produce conditions conducive to bacterial overgrowth, setting up a situation as described above resulting in intestinal damage secondary both to the bacterial overgrowth and to the metabolism of alcohol by these bacteria to toxic products. When considering the effects of ethanol on the small intestine, one must also consider its effect on other organs such as the pancreas, stomach, and liver, in that intestinal absorption is a complex process, and, for many nutrients, dependent on alterations of physiologic homeostasis controlled by other organs. For example, although the effect of ethanol may be to reduce the absorption of a substance, this effect may be secondary to damage to the pancreas with resultant inadequate release of pancreatic factors necessary for intestinal absorption. In addition, when considering alcohol, it is necessary to also consider malnutrition *per se*, since alcoholism is often accompanied by poor nutrition which in itself contributes to damage of alimentary tract organs.

It is becoming increasingly apparent that ethanol exerts diverse effects on small intestinal function. It stimulates intestinal synthesis of triglycerides and cholesterol, as well as production of very low density lipoproteins (*1–3*). Although acute ethanol administration stimulates lipid absorption, chronic ethanol ingestion inhibits its absorption (*4*). Ethanol also stimulates activities of jejunal adenylate cyclase (*5*) and pyruvate kinase (*6*) while diminishing ATP content (*7*) and activites of hexokinase, fructose-1-phosphate aldolase, fructose-1,6-diphosphate aldolase, and fructose-1,6-diphosphatase activity (*6*). Ethanol has been shown to interfere with the ability of different segments of small intestine to absorb amino acids (*8–10*), carbohydrates (*8, 11, 12*), vitamin B_{12} (*13, 14*), and thiamine (*15*). There is lack of agreement regarding the effect of alcohol, folate deficiency, and protein deficiency on intestinal folate absorption (*16, 17*). Ethanol interferes with small intestinal absorption of sodium and water, perhaps by changes related to ATP or ATPase content (*12, 18–20*). The intestinal

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transport of manganese is increased by ethanol administration (*21*), but ethanol inhibits the absorption of calcium (*22*).

The association of ethanol ingestion and intestinal calcium transport represents a prototype for the type of problem involved when evaluating effects of toxicants on intestinal function. Malabsorption of calcium in chronic alcoholic patients may be secondary to steatorrhea, producing inadequate absorption of fat soluble vitamin D. This steatorrhea may be a result of the effects of ethanol on organs other than the intestine. Thus, in alcoholics, steatorrhea may be secondary to pancreatic exocrine insufficiency, impaired micellar solubilization as a result of reduced conjugated bile salt concentrations due either to decreased bile salt synthesis, cholestasis, or the effects of intestinal bacterial overgrowth, or small intestinal lesions produced by folate and/or other nutritional deficiencies. Krawitt has examined the hypothesis that ethanol interferes with calcium at the intestinal level, and has shown that *ethanol ingestion interferes with the ability of rat* intestine to transport calcium independently of starvation as well as hepatic and pancreatic dysfunction (*22–25*). Acute administration of high concentrations of ethanol caused a significant decrease in the ability of duodenal gut sacs to transport calcium, while no effect is apparent after intraperitoneal administration of ethanol (*23*). When 7.5 g/kg body weight of ethanol was given intragastrically 1 hr before measuring transport by everted gut sacs, a significant reduction in transport was noted while no effect was apparent after intraperitoneal administration of ethanol. Histologically, the duodenum from rats receiving intragastric ethanol demonstrated necrosis of the villus epithelium and infiltration of lymphocytes and plasma cells in the remaining crypts. When ethanol was added directly to the incubation system in vitro, concentration of 0.1% and 1.0% ethanol did not diminish transport ratios while 1.5% and 2.6% solutions significantly inhibited calcium transport. Equiosmolar solutions of mannitol, an inert molecule, reduced transport ratios to unity while an initially equiosmolar solution of glucose, a metabolically active substance, resulted in no interference in transport. Histological examination of the gut sacs after incubation similarly revealed destruction of villus architecture with sloughed and shrunken epithelial cells containing granular vacuolated cytoplasm and pigmented nuclei in the presence of percentages of ethanol which inhibited transport. Results of these experiments suggest that ethanol inhibition is a manifestation of local toxicity to mucosa, which is in part due to the hypertonic nature of the solution. That this defect could be relatively rapidly reversed was apparent from other experiments: calcium transport measured 18 hr after a single intragastric dose of ethanol showed no effect on transport ratios (*22*).

The mechanism underlying suppression of intestinal calcium transport by chronic ethanol ingestion appears to differ from that observed after acute administration, for under conditions of chronic administration no evidence of histologic changes were observed by light microscopy when rats were raised on a laboratory diet and given 20% ethanol in water as a sole source of fluid for 12 days (*22*). Ultrastructural examinations, however, revealed mitochondrial changes with occasional intramitochondrial inclusions, a paucity of rough endoplasmic reticulum, and Golgi apparatus containing greatly dilated cisternae (*24*). In addition, these intestinal cells contained electron-dense calcium-containing granules within the microvilli as seen in other conditions in which duodenal calcium transport is inhibited. This regimen of chronic ethanol ingestion *interfered with the ability of rat duodenum to transport* calcium compared with *ad libitum* or pair-fed controls (*22, 25*) as measured by everted gut sacs, although no differences were noted in jejunal or ileal concentration ratios (*22*, Krawitt et al., unpublished data), suggesting that this defect is limited to the duodenum, the segment of small intestine that absorbs calcium most avidly. The administration of vitamin D_2, vitamin D_3 or 25-hydroxyvitamin D_3, a polar metabolite resulting from the hydroxylation of vitamin D_3 in the liver, did not restore the ability of duodenal gut sacs to transport calcium (*25*). Similarly, when 1,25-dihydroxyvitamin D_3, the active metabolite of vitamin D which is formed by hydroxylation of 25-hydroxyvitamin D_3 by the kidney, was administered to animals ingesting ethanol, no reversal of the ethanol-induced inhibition of transport capacity was observed (*24*). Taken together, these results suggest that ethanol inhibition is mediated at the intestinal level, affecting mechanisms that are probably independent of vitamin D but might interfere with subcellular location of the active metabolite or with its action after localization to the cell nucleus. In view of the evidence that ethanol affects a variety of intestinal cell metabolic and transport processes as noted above, however, it appears more likely that the inhibition results from an effect on small intestinal transport independent of the vitamin D pathway. This regimen of ethanol ingestion had no effect on the levels of intestinal proteins which have been proposed as possibly playing a functional role in the translocation of calcium in the small intestine: no significant difference in the assay of a crude vitamin D-dependent calcium-binding

protein preparation was noted comparing ethanol-fed to control animals (*25*). Levels of brush border alkaline phosphatase were depressed in animals ingesting ethanol as compared to *ad libitum* controls; duodenal alkaline phosphatase activity from pair-fed starved animals was also depressed. Levels of Ca ATPase and Mg ATPase were not affected. In order to correlate these findings with *in vivo* measurements, the effect of this regimen of chronic ethanol ingestion was investigated utilizing a balance technique in conjunction with *in vitro* studies measuring calcium transport by evert gut sacs (Krawitt et al., unpublished observations). *In vivo*, net calcium absorption was suppressed in animals ingesting ethanol as well as in partially starved pair-fed controls, emphasizing once again the importance of evaluating the contribution of malnutrition to alcohol-associated malabsorption. It is evident that when evaluating the effects of this toxicant, its effects in producing generalized malnutrition, depressing pancreatic and hepatic function as well as effects on glucocorticosteroid, parathyroid or intestinal hormone homeostasis must be considered in addition to the direct toxic effects on intestinal epithelial cells.

E. L. Krawitt was the recipient of Public Health Service Academic Career Development Award K07 35234. These studies were supported in part by Research Grants AM 14686 and AM 16052.

This material is drawn from a Background Document prepared by the author for the NIEHS Second Task Force for Research Planning in Environmental Health Science. The Report of the Task Force is an independent and collective report which has been published by the Government Printing Office under the title, "Human Health and Environment—Some Research Needs." Copies of the original material for this Background Document, as well as others prepared for the report can be secured from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, Virginia 22161.

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