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Part II Urea hydrolysis and ammonia absorption in upper and lower gut lumen and the effect of neomycin

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The purposes of the present study in patients with cirrhosis are to investigate and compare *in vivo* urease activity in the upper and lower portions of the gastrointestinal tract, as reflected by the hydrolysis of urea to ammonia in the gut lumen and the subsequent change in blood ammonium concentrations. The antibiotic effect of neomycin on these processes was assessed to evaluate relative contributions and locations of mucosal and bacterial urease activity. In addition, transfer of ammonia to the circulation from the upper and lower parts of the gastrointestinal tract was compared, both before and after treatment with the antibiotic.

MATERIAL AND METHODS

Patients with cirrhosis of the liver were studied, since in this condition measurable changes in the ammonium concentration of the peripheral blood follow administration of ammonium salts or urea into the gastrointestinal tract. The diagnosis was confirmed by hepatic biopsy in all of the 17 participants. Fifteen were chronic alcoholics and two had a previous history consistent with hepatitis; they comprised 10 males and seven females whose ages ranged from 39 to 62 years (mean 52 years). All had moderately severely impaired hepatic function. Six were jaundiced, four had ascites, six gave a history of previous coma, and eight had earlier experienced massive gastro-

intestinal bleeding; portal-systemic anastomosis had been carried out in four. In addition, 10 individuals (four with cirrhosis of the alcoholic) were studied to quantitate fluctuations in fasting blood ammonium concentrations for control purposes.

Ammonia and urea tolerance tests were performed in the fasting state, urea or ammonium acetate being given by mouth or by rectum. When comparison of responses to the various tests was made, paired data from patients who had undergone both the relevant studies were analysed. Ammonium acetate was administered by mouth or by rectum in a dose of 5 g. dissolved in 450 ml. of tap water (ammonia nitrogen equivalent 0.9 g., pH 7.0, osmolality 204 mOsm.). The enema was retained for a minimum of one hour. Urea (AR) was administered by mouth or by rectum in a dose of 20 g. dissolved in 700 ml. of tap water (ammonia nitrogen equivalent 9.3 g., pH 7.6, osmolality 455 mOsm.). The enema was retained for a minimum of two hours. Following these studies, neomycin (2.0 g. four times daily for 48 hours) was given, and the various tests were repeated within 48 hours.

After patients had fasted overnight, venous blood was taken immediately before and at half-hour intervals (for two hours) after the administration of ammonium acetate, and also before and at hourly intervals (for four hours) after the administration of urea. Blood ammonium concentrations were measured by a modification (Reinhold and Chung, 1961) of the method of Seligson and Hirahara (1957), 4 ml. of Nessler's reagent was used, and determinations were made after five minutes at 415 m μ with the Bausch and Lomb Spectronic 20 colorimeter. The error of the method with duplicate samples was $\pm 3\%$.

RESULTS

Mean blood ammonium concentrations did not change significantly during fasting over a four-hour period in control individuals. The mean initial blood ammonium concentration was 47 (S.E. ± 11.4) μ g.

ammonia nitrogen per 100 ml. blood (Table), and the mean of the greatest rise during fasting in each patient (peak less initial values for each patient) was 47.9 μ g. (S.E. ± 9.6) ammonia nitrogen per 100 ml. of blood.

In patients with cirrhosis who were given ammonium acetate either by mouth or by rectum, the elevations in blood ammonium concentration (peak less initial value) were significantly ($p < 0.001$) greater than those in fasting individuals (Table). A comparable increase in blood ammonium concentration also followed the administration of urea by rectum ($p < 0.001$); by contrast, no significant change in blood ammonium concentration occurred when the same amount of urea was given by mouth (Table). The degree of hyperammonaemia following ammonium acetate given by mouth or by rectum was similar (Table, Fig. 1); urea given by rectum caused a significantly higher ($p < 0.001$) mean peak less initial blood ammonium concentration than did urea given by mouth (Fig. 1).

Treatment with neomycin had no significant effect on the blood ammonium concentrations resulting from administration of ammonium acetate by mouth or by rectum, nor on those following urea given by mouth (Table I, Fig. 1). By contrast, mean peak less initial blood ammonium concentrations following urea given by rectum was significantly lower than that present before the same patients had received neomycin ($p < 0.005$); in fact, the results after neomycin did not differ significantly from those of fasting control individuals or those receiving urea by mouth (Table).

Peak concentrations of blood ammonium occurred between 30 and 60 minutes after the administration of ammonium acetate, whether the drug was given by mouth or by rectum, and this pattern was not

TABLE

MEAN BLOOD AMMONIUM CONCENTRATIONS BEFORE AND AFTER ADMINISTRATION OF UREA OR AMMONIUM ACETATE AND EFFECT ON THEM OF NEOMYCIN

Test No.	Circumstances	No. of Individuals Studied	Blood Ammonium Concentration (μ g. $\text{NH}_3\text{N}/100$ ml.)	
			Initial ($\pm$ S.E.)	Peak less Initial ($\pm$ S.E.)
1	Fasting (4 hours) control individuals	10	47 $\pm$ 11.4	26 $\pm$ 8.2
2	Cirrhosis: ammonium acetate or urea tolerance			
	Ammonium acetate by mouth	12	71 $\pm$ 15.4	239 $\pm$ 42
	Ammonium acetate by rectum	14	53 $\pm$ 13.4	288 $\pm$ 36
	Urea by mouth	12	50 $\pm$ 11.8	78 $\pm$ 20
	Urea by rectum	8	63 $\pm$ 12.7	238 $\pm$ 19
3	Cirrhosis: tolerance tests before and after neomycin ¹			
			Before Neomycin	After Neomycin
	Ammonium acetate by mouth	9	226 $\pm$ 40	265 $\pm$ 28
	Ammonium acetate by rectum	7	292 $\pm$ 34	214 $\pm$ 30
	Urea by mouth	9	82 $\pm$ 19	84 $\pm$ 14
	Urea by rectum	6	239 $\pm$ 19	52 $\pm$ 12

¹Peak less initial ($\pm$ S.E.)

FIG. 1. Blood ammonium and urea concentrations given by mouth and by rectum before and after neomycin.

influenced by neomycin (Fig. 1). The peak blood ammonium concentration following the administration of urea by rectum occurred one to two hours after the compound had been given and declined less abruptly (Fig. 1).

When ammonium acetate was given by mouth, nausea was common and three patients vomited. Despite comparable hyperammonaemia (Fig. 1), the only complaint after ammonium acetate was given by rectum was mild lower abdominal discomfort after the enema. Urea given by mouth caused no symptoms. After urea was given by rectum, the patient who had the highest blood ammonium concentration (572 µg./100 ml.) also experienced transient impending hepatic coma; the majority experienced lower abdominal discomfort following the enema.

DISCUSSION

Whether ammonia was absorbed from the upper or lower part of the gastrointestinal tract, transfer to the systemic circulation was shown to result in comparable hyperammonaemia. Urea given by rectum also caused hyperammonaemia, although the same amount given by mouth did not affect blood ammonium concentrations. Hyperammonaemia following the administration of urea by rectum was attributed to liberation of ammonia from the urea by bacterial urease in the gut lumen, since the response was abolished by the antibiotic neomycin, which does not inhibit urease directly (Belding and Kern, 1963). There was no evidence that the absorptive defect sometimes induced by the drug (Jacobson and Falcon, 1961) affected ammonia, since blood ammonium concentrations after ammonium acetate was given were not influenced by neomycin.

The failure of urea administered by mouth to cause hyperammonaemia was surprising, since mucosal urease activity is much higher in the upper part of the gastrointestinal tract than in the ileum and large bowel (Fossel, 1948; Aoyagi *et al.*, 1966). Moreover, increased concentrations of ammonia in blood and gastric juice have been reported when urea has been given by vein, the inference being that urea diffuses from blood to mucosal cells and is there hydrolyzed to ammonia, which enters the circulation or the stomach (Rappoport and Kern, 1963; Fleshler and Gabuzda, 1965). Our findings imply insufficient contact between substrate and mucosal enzyme to raise blood ammonia concentrations significantly when the amount of urea used is delivered into the lumen of the upper part of the gastrointestinal tract. The contrasting elevations of blood ammonium concentrations (and, in one instance, the development of hepatic coma) which resulted from the same amount of urea given by rectum indicate that bacterial urease is not subject to the same limitation and is a principal factor in hydrolysis of urea in the gut. It follows also that bacterial urease activity in the upper part of the gastrointestinal tract in cirrhosis is seldom sufficient to cause hyperammonaemia, although the flora may be abnormal and increased in such patients (Martini, Phear, Ruebner, and Sherlock, 1957).

The findings in this study and in an investigation *in vitro* carried out concurrently (Aoyagi *et al.*, 1966), seen in perspective with other reports (Fossel, 1948; Kornberg *et al.*, 1954; Kornberg and Davies, 1955; Walser and Bodenlos, 1959; Conway *et al.*, 1959; Rappoport and Kern, 1963; Visek and Thomson, 1964), indicate that both mucosal and

bacterial urease are present in the gastrointestinal tract of man. The morphogenetic effects of the gut flora (Dubos and Schaedler, 1964), as well as the possibility of contamination and the difficulty of complete separation, impede identification of the mucosal or bacterial origin of enzymes in the bowel. However, the stomach and jejunum contain the highest mucosal concentrations of urease in the gastrointestinal tract (Fossel, 1948; Aoyagi *et al.*, 1966), yet are normally sterile or harbour only a scanty bacterial flora (Cregan and Hayward, 1953). By contrast, urease-producing bacteria abound in the colon (Cregan and Hayward, 1953; Rosebury, 1962; Donaldson, 1964), where concentrations of the enzyme in mucosal homogenates from the human large intestine are relatively low (Fossel, 1948; Aoyagi *et al.*, 1966). The urease activity measurable under the circumstances of the present study was bacterial in origin and was confined to the lower part of the gastrointestinal tract. These conclusions accord with the work of Silen, Harper, Mawdsley, and Weirich (1955) in animals and also that of Walser and Bodenlos (1959), who estimated that approximately 20% of urea produced in humans was hydrolyzed by urease and that the process was strikingly reduced by the administration of neomycin. It is therefore likely that bacteria in the gastrointestinal tract are largely responsible for the degradation of endogenous, as well as exogenous, urea.

The proportion of ammonia derived from urease activity in patients with hyperammonaemia cannot be specified, but is presumed greatest in those with cirrhosis and azotaemia (Baldus, Feichter, and Summerskill, 1964; Webster and Gabuzda, 1959). Our results support the rationale of therapeutic measures aimed specifically at reducing urease activity in certain instances of the hepatic coma syndrome. However, for maximal benefit, urease inhibition (Fishbein and Carbone, 1964; Aoyagi and Summerskill, 1966) or immunity (Thomson and Visek, 1963; Visek and Thomson, 1964) may require that effects on both mucosal and bacterial enzymes be established, especially since uncertainty about the identity of ureases from each source (Nikiloff, 1959; Guo and Liu, 1965) may limit the specific effects of both procedures. For sustained reduction of bacterial urease activity in the gut, colonization of the colon with lactobacillus (Macbeth, Kass, and McDermott, 1965), which is urease negative, may also diminish liberation of ammonia from endogenous urea. The use of neomycin for treating hyperammonaemia and hepatic coma (Butt and Summerskill, 1961; Chalmers, 1960) is also supported by this study, since a short course of the drug abolished measurable urease activity.

SUMMARY

Urease activity within the gut, as reflected by blood ammonium concentrations following the administration of urea by mouth or by rectum to patients with cirrhosis, is measurable only in the lower part of the gastrointestinal tract. It is principally bacterial in origin and is abolished by the administration of neomycin. Transfer of ammonia from the upper or lower part of the gastrointestinal tract to the circulation results in comparable degrees of hyperammonaemia and is not influenced by neomycin.

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The October 1966 Issue

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