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Increased glycine absorption rate associated with acute bacterial infections in man

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1. Glycine absorption rate from a 300 mm jejunal segment was determined in vivo in four Zambian African subjects with acute, and four with chronic, respiratory infections. Glycine solutions (100, 150 and 250 mmol/l) were perfused, by means of a double-lumen tube technique. The results were compared with those for four relatively normal Zambian African subjects ('reference' group) previously studied. The group with acute-infections had a significantly higher mean absorption rate than the reference or chronic-infection group.

2. Glycine absorption results from a 100 mmol/l glycine solution in an additional twenty-four Zambian African subjects have also been analysed. When results for the thirty-six subjects were combined, those with acute bacterial infections had a significantly higher mean absorption rate than the normal subjects or those with chronic infections. For the twenty-one normal subjects there was a significant positive correlation between the individual absorption rates and serum total globulin and γ-globulin concentrations.

3. It seems likely that the rapid catabolism of protein associated with infection is counteracted by an increase in amino acid absorption rate. In subjects on a low-protein diet that mechanism would be limited. The deterioration in nutritional status during infections in developing countries could therefore be partly explained by the present observation.

In Zambian African subjects there is a significant reduction in the rate of glucose absorption in the presence of systemic bacterial infections such as lobar pneumonia or pulmonary tuberculosis (Cook, 1971*a*). A significant reduction in the weight of D-xylose excreted in the urine after a 25 g dose given by mouth has been demonstrated in association with similar infections (Cook, 1972*a*). It is important to determine whether the absorption of amino acids and peptides is impaired by infections.

In the present investigation, using a double-lumen tube jejunal-perfusion system in vivo, the rate of glycine absorption in Zambian African subjects with acute bacterial lobar pneumonia or chronic respiratory infections has been studied. Results obtained while infusing glycine solutions (100, 150 and 250 mmol/l) into the upper jejunum of those subjects have been compared with results previously obtained in a relatively healthy reference group of Zambian African subjects (Cook, 1972*c*). In addition, previous results obtained for rate of absorption of glycine from a 100 mmol/l glycine solution have been analysed for a larger group of subjects, with and without systemic bacterial infections (Cook, 1971*b*, 1972*b*, *c*, 1973).

EXPERIMENTAL

Subjects studied

Table 1 gives details of the subjects. Eight male Zambian African subjects, all of whom were in-patients at The University Teaching Hospital, Lusaka, were studied

Table 1. *Details of the eight Zambian African subjects*

Subject no.	Group	Age (years)	Body-wt (kg)	Tribe*	Clinical diagnosis	Haemoglobin (g/l)	Serum protein (g/l)			Stool parasites	Tube position (distance of proximal opening past ligament of Treitz) (mm)
							Albumin	Total globulin	γ-Globulin		
1	Acute infection	24	56	Tumbuka	Left lower lobar pneumonia	145	29	51	27	ND	210
2		45	52	Soli	Right upper, mid, and lower lobar pneumonia	123	23	46	20	None	300
3		28	54	Chewa	Left lower lobar pneumonia	149	33	43	21	ND	310
4		40	59	Chewa	Right upper lobar pneumonia	135	26	40	19	None	150
5	Chronic infection	55	63	Tumbuka	Right upper lobar pneumonia (unresolved)	110	32	49	28	Hook-worm	280
6		50	56	Ngoni	Right upper lobar pneumonia (unresolved)	134	22	46	20	None	120
7		36	44	Tumbuka	Pulmonary tuberculosis	102	26	46	20	None	180
8		52	56	Lenje	Pulmonary tuberculosis	81	31	56	39	Hook-worm	60

ND, not determined.
* Brelsford (1965).

after the procedure and purpose of the study had been explained. None of the subjects was clinically malnourished or suffered from gastro-intestinal disease. They all had severe systemic bacterial infections; four had bacterial lobar pneumonia (acute-infection group) and four had chronic respiratory infections (chronic-infection group). The mean lengths of the clinical histories in the two groups were 5 (4–9) d and 49 (21–70) d respectively. All of the diagnoses were confirmed by chest radiology. Sputum examination in subjects 7 and 8 repeatedly gave positive results for *Mycobacterium tuberculosis*, and in subject 2 for pneumococci. Subject 2 had hepatocellular jaundice associated with his severe bacterial infection. Table 1 also gives results for haemoglobin, serum protein (Cook, 1972*a*) and stool parasites. Results for four subjects studied by Cook (1972*c*) are included in the analysis. They were relatively healthy Zambian African subjects ('reference' group), although two had mild respiratory infections: in one acute broncho-pneumonia and in the other unilateral apical pulmonary tuberculosis.

Table 2 gives details of thirty-six subjects who were given jejunal perfusions with a 100 mmol/l glycine solution. Twelve of them have been described above. In previous investigations (Cook, 1971*b*, 1972*b*, *c*, 1973) an additional twenty-four Zambian African subjects (two with acute bacterial lobar pneumonia, three with chronic bacterial infections, and nineteen with no evidence of an infective disease) were studied. They came from a wide variety of Zambian tribes (Brelsford, 1965). One of the two subjects in the reference group (see above) who had a mild respiratory infection is included in the acute- and the other in the chronic-infection group. Values for absorption rates in those subjects have been analysed, especially with a view to determining whether glycine absorption rates in them were related to any of the clinical or biochemical indices tested.

Perfusion technique

The perfusion studies were carried out as previously described (Cook, 1971*a*, *b*). A double-lumen tube was swallowed on the evening before the test, and all investigations were performed after a 14–18 h overnight fast during which sips of water were permitted. The perfusing solution was pumped at a constant rate of 12·0 ml/min from the proximal opening of the tube, and the intestinal contents were siphoned out through the other lumen 300 mm further on. After an equilibration period of 35 min, three successive 10 min collections of fluid were obtained. They were immediately frozen and stored. The position of the tube was checked radiologically before (Table 1) and after the studies; in no subject had the proximal (infusion) opening moved by more than 60 mm in a distal direction at the end compared with the beginning of the study. The solutions which were infused contained (*a*) 100 mmol/l, (*b*) 150 mmol/l, and (*c*) 250 mmol/l glycine. They were all made iso-osmotic with sodium chloride and they contained 5 g/l polyethylene glycol (PEG) 4000 as a non-absorbable marker. All the solutions were infused in ascending order of glycine concentration, and followed immediately after each other.

Table 2. *Summary of clinical and biochemical details of the Zambian African subjects who received* 100 *mmol/l glycine perfusions*

(Mean values; ranges are shown in parentheses)

Group	No. studied	Sex ♂	Sex ♀	Age (years)	Body-wt (kg)	Haemoglobin (g/l)	Serum protein (g/l) Albumin	Serum protein (g/l) Total globulin	Serum protein (g/l) γ-Globulin	Tube position (distance of proximal opening past ligament of Treitz) (mm)
Acute infection	7	7	0	37 (24–65)	57 (40–70)	134 (120–149)	30 (23–37)	41 (21–60)	20 (9–36)	200 (120–310)
Chronic infection	8	6	2	40 (18–56)	53 (44–63)	102 (69–139)	29 (22–37)	47 (36–57)	23 (15–39)	130 (10–290)
'Normal'	21	16	5	38 (16–66)	53 (39–70)	123 (39–167)	36 (24–44) ($n = 20$)	39 (28–52) ($n = 20$)	19 (15–26) ($n = 20$)	170 (10–360)

Analytical methods and calculation of results

Glycine was estimated by the colorimetric method of Giroux & Puech (1963), and PEG by the turbidimetric method of Hydén (1955). All perfusion solutions were treated in exactly the same way as the intestinal samples; glycine and PEG were estimated in triplicate and duplicate respectively. Glycine and net water absorption rates were calculated from standard formulas (Cook, 1971*b*). Reproducibility values for glycine and net water absorption rates for the three 10 min collections during each perfusion are as follows (Cook, 1972*b*). Glycine ($n = 24$): SD = 11·2 mg/min per 300 mm of jejunum; coefficient of variation = 12·2%. Water ($n = 24$): SD = 1·02 ml/min per 300 mm of jejunum.

RESULTS

Glycine absorption rates and kinetic curves

All the subjects, with the exception of no. 3, had diarrhoea towards the end of or after his investigation. It consisted of one to three fluid stools within 2 h of completion of the perfusion.

Fig. 1 gives the mean absorption rates for glycine in the acute-infection, chronic-infection, and reference groups, from the various glycine solutions. The acute-infection group had significantly higher rates than the reference group during the 100 and 150 mmol/l perfusions ($t = 5·65$, $P < 0·01$ and $t = 8·66$, $P < 0·001$ respectively). The acute-infection group also had significantly higher rates than the chronic-infection group during the 100, 150 and 250 mmol/l perfusions ($t = 2·97$, $P < 0·05$; $t = 3·46$, $P < 0·02$; and $t = 2·98$, $P < 0·05$ respectively). Although the mean results for the chronic-infection group were higher than those for the reference group, the differences were not significant. The kinetic curves for the three groups have been plotted. Fig. 1 also gives mean net water absorption rates for each group at each glycine concentration in the perfusing fluid; none of the differences between the three groups was significant.

Fig. 2 shows Lineweaver & Burk (1934) plots for the mean glycine absorption rates in the three groups. For each group an approximately straight line is obtained. Table 3 summarizes the V_{max} and K_t values for glycine, calculated from those plots, under the conditions of the investigation.

Glycine absorption rates during a 100 mmol/l glycine infusion

Fig. 3 shows glycine absorption rates in the thirty-six subjects studied. The difference between the means for the subjects in the normal group and those with acute infections ($t = 3·37$; $n = 28$; $P < 0·01$) was significant, as was the difference between the means for the subjects with acute and chronic infections ($t = 2·28$; $n = 15$; $P < 0·05$). The difference between the values for the normal subjects and those with chronic infections was not significant. The two lowest values for the subjects with chronic infections were associated with pulmonary tuberculosis and chronic pulmonary fibrosis respectively. For the normal subjects the clinical diagnoses for

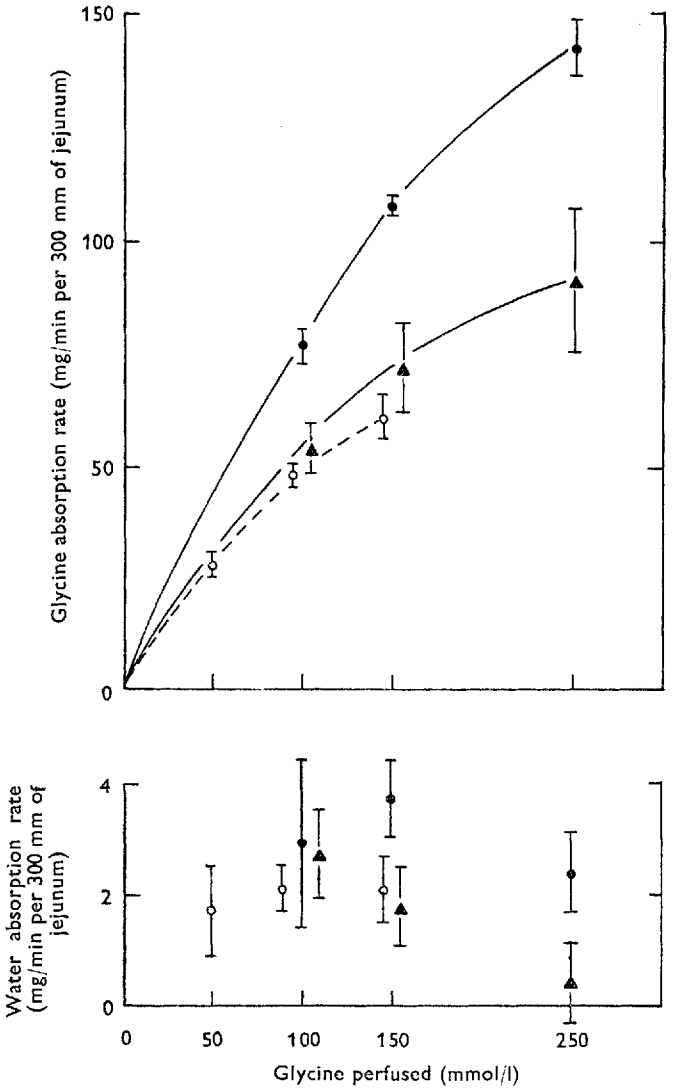

Fig. 1. Mean glycine and net water absorption rates in the three groups of Zambian African subjects studied in the main part of the investigation. Mean values with their standard errors are shown for each point. ●, acute-infection group; ▲, chronic-infection group; ○, reference group previously studied by Cook (1972*c*).

those who had an absorption rate of less than 40 mg/min per 300 mm of jejunum were: recovered mild upper respiratory tract infection (16 mg/min per 300 mm of jejunum), recovered acute gastroenteritis (two subjects), an anxiety state, and undiagnosed abdominal pain. Table 4 gives results for the tests of correlation between the glycine absorption rates in the twenty-one normal subjects studied, and the clinical and biochemical indices examined. Positive correlations between the individual glycine absorption rates and the serum total globulin and γ-globulin concentrations were

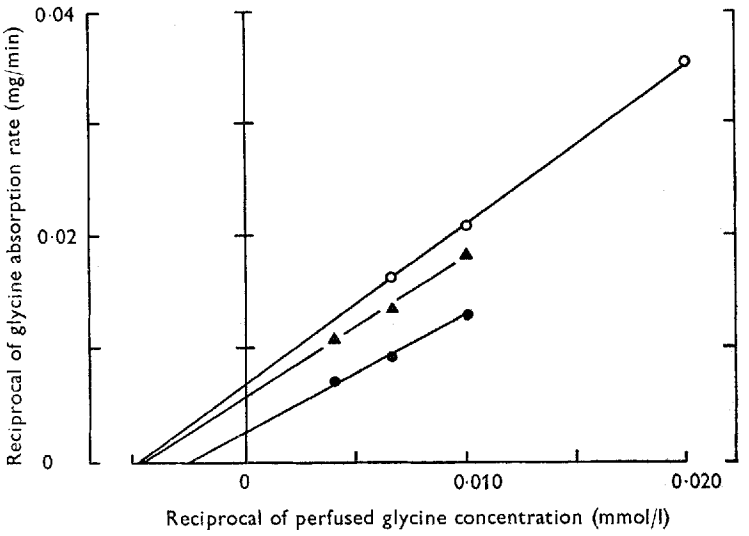

Fig. 2. Lineweaver & Burk (1934) plot of the mean glycine absorption rates during the glycine perfusions in the three groups of Zambian African subjects. ●, acute-infection group; ▲, chronic-infection group; ○, reference group. The calculated results for V_{max} and K_t are shown in Table 3.

Table 3. *V_{max} and K_t values for the three groups of Zambian African subjects**

Group	V_{max} (mg/min per 300 mm of jejunum)	K_t (mmol/l)
Acute infection	417	435
Chronic infection	179	227
'Normal'	149	213

* These results are calculated from the Lineweaver–Burk plots shown in Fig. 2.

significant. The correlations between the absorption rates and serum albumin concentrations were not significant.

DISCUSSION

This investigation clearly shows that subjects with bacterial lobar pneumonia have a significantly increased mean rate of glycine absorption from the jejunum at the concentrations tested, compared with subjects without infections or with mild infections (reference group) (Fig. 1). The results for the eight subjects in the main part of the present study are supported by the analysis of values for a further twenty-eight subjects, making a total of thirty-six subjects, who were perfused with a 100 mmol/l glycine solution (Fig. 3). Subjects with chronic bacterial infections of the respiratory system did not have a significantly increased mean absorption rate compared with the subjects without infections. The mean rate however was slightly higher in the chronic-infection group. Whether the increase in glycine absorption rate associated with acute bacterial infections also applies to other amino acids and to peptides has not been

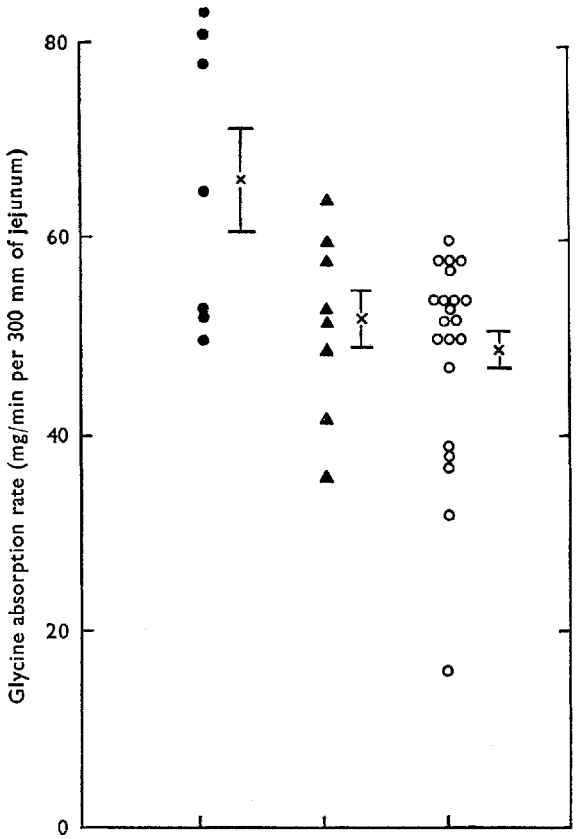

Fig. 3. Glycine absorption rate from a 100 mmol/l glycine solution in Zambian African subjects with acute infections (●) or chronic infections (▲) and in the normal group (○). Mean values with their standard errors are shown for each group.

Table 4. *Tests of correlation for absorption rates from the* 100 *mmol/l glycine solution and the clinical and biochemical indices of the 'normal' Zambian African subjects**

No. studied	Age (years)	Body-wt (kg)	Serum protein (g/l)			Tube position (distance in mm of proximal opening past ligament of Treitz)
			Albumin	Total globulin	γ-Globulin	
21	$r = -0.14$	$r = +0.01$	$r = +0.29$	$r = +0.61$	$r = +0.49$	$r = -0.18$
	$n = 21$	$n = 21$	$n = 20$	$n = 20$	$n = 20$	$n = 21$
	NS	NS	NS	$P < 0.01$	$P < 0.05$	NS

NS, not significant.

* The coefficient of linear correlation (r), and the number of studies (n), are shown for each index.

investigated. Glycylglycine (the dipeptide of glycine) seems to be transferred by a mechanism different from that used by glycine (Cook, 1973).

The results for the eight subjects in the main study confirm a previous finding (Cook, 1972*c*) that glycine absorption in man conforms to saturation kinetics. The Lineweaver–Burk plots of the mean results gave straight lines for both the acute- and chronic-infection groups (Fig. 2).

The mechanism that produces the increased absorption rate of glycine is unknown. It is presumably part of a homoeostatic mechanism designed to conserve amino acids during the rapid catabolic phase of protein utilization in the presence of bacterial infections. When the intake of protein is low, physiological mechanisms in both rats and children adapt to conserve nitrogen and alter the pattern of protein synthesis (Waterlow, 1968). Although an increase in the rate of amino acid absorption in the presence of malnutrition or starvation has been reported by some investigators, other studies indicate either no effect, or even an inhibition of absorption. Those studies were made in both experimental animals (Kershaw, Neame & Wiseman, 1960; Hindmarsh, Kilby, Ross & Wiseman, 1967; Kirsch, Saunders & Brock, 1968; Steiner & Gray, 1969; Newey, Sanford & Smyth, 1970; Neale, 1971; Wiseman, 1971) and in man (Steiner, Farrish & Gray, 1969; Adibi & Allen, 1970). The present results suggest that there is a stimulus associated with the very high catabolic rate during acute infections which leads to an increased rate of glycine absorption. The subjects in the present study with chronic infections presumably had a slightly raised rate of amino acid catabolism, but the rate of glycine absorption was not significantly increased compared with that in normal subjects.

The findings in the present study are the reverse of those of Cook (1971*a*) for glucose absorption rate in the presence of bacterial infections. In that study, the glucose kinetic curve for subjects with acute or chronic infections was significantly flattened compared with the curve for a group of subjects without infections ($P < 0{\cdot}02$). Similarly a reduction of absorption of D-xylose in the presence of infection has been demonstrated; xylose probably shares the same transport mechanism as glucose (Crane, 1968). Glucose absorption in Zambian African subjects seems to be confined to the first 400–500 mm of the proximal jejunum (Cook and Snook, unpublished observations).

Whether the present observation has a practical importance in human nutrition is unknown. The study suggests that amino-acid conservation, which is known to occur in bacteria (Waterlow, 1968), is teleologically a basic compensatory mechanism; glucose absorption rate does not, however, seem to adapt satisfactorily to infections. The site of glycine absorption from the human small intestine has not been accurately delineated, although methionine has been shown to be absorbed at a much higher rate from the proximal than from the distal small intestine in man (Schedl, Pierce, Rider & Clifton, 1968). The 'reserve' capacity for glycine absorption from the human jejunum is obviously limited; all except one of the subjects in the main part of the present investigation had diarrhoea, presumably of an osmotic nature, after the glycine perfusions. This occurred both in the acute-infection group, where there was a very high absorption rate, and in the chronic-infection group. There was not a significant corre-

lation between the position of the tube and the glycine absorption rate in the subjects investigated in the present study. It seems likely that the absorption site for glycine is not limited to a short segment of proximal jejunum, as has been shown for glucose (Cook and Snook, unpublished observations).

If the present observation applies to other amino acids, it may be of relevance to infant malnutrition in Zambia and other developing countries. The adaptive response of increased rate of amino acid absorption in the presence of infections would come into operation during an acute respiratory infection. Absorption of glucose, and probably of other carbohydrate, upon which most children in the developing world subsist, is likely to be impaired during that period. Thus the child who normally survives on a diet high in carbohydrate and marginally adequate in protein would be thrown off balance by the infection; overt malnutrition could result. The infant with an acute bacterial infection in a highly developed country would presumably get his additional energy from protein (through amino acids) to counteract the high rate of catabolism associated with the infection.

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