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THE TRANSPORT OF URIC ACID ACROSS MOUSE SMALL INTESTINE *IN VITRO*

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SUMMARY

1. The *in vitro* recirculation technique was used to study the uptake and transport of uric acid by the jejunum of mouse small intestine.

2. Three components of the serosal secretions appeared to be endogenously derived nucleic acid derivatives; two of these were identified as uric acid and uracil. There was no detectable metabolism of uric acid by the intestine.

3. Uric acid transported from the lumen appeared in the serosal fluid at a concentration higher than that in the lumen. The final serosal/luminal concentration ratio of about 1·18 for exogenous uric acid was found to be constant over the concentration range studied (0·01–0·1 mM). The presence of exogenous uric acid in the lumen did not affect the production of endogenous uric acid by the intestine and its release into the serosal secretions.

4. Mucosal concentration of exogenous uric acid was below, but the total mucosal concentration (exogenous + endogenous) was above, that in the lumen. There was no evidence for the secretion of endogenous uric acid into the lumen.

5. Oxypurinol significantly decreased the rate of serosal appearance of exogenous uric acid.

6. Allopurinol did not affect the transport of exogenous uric acid from the lumen and there was negligible metabolism of allopurinol to oxypurinol by the tissue.

7. Uracil did not affect the transport of exogenous uric acid from the lumen, or the serosal appearance of endogenous uric acid. Likewise uracil transport was unaffected by luminal uric acid.

INTRODUCTION

The size of the body pool of uric acid (the end product of purine metabolism in man (Rundles, Wyngaarden, Hitchings & Elion, 1969)) is governed by the balance between the exogenous and endogenous sources and the excretion or metabolism of uric acid.

The sources of exogenous uric acid are the purines and purine precursors present in the diet (Clifford & Story, 1976). In man over-production of uric acid and its deposition, as crystals, results in the disease gout (Wyngaarden, 1965). If the factors

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affecting the alteration in serum uric acid levels associated with this disorder are to be fully understood, knowledge of all the sources of serum uric acid is obviously required.

Previous work has been concerned primarily with enzyme function and the control of the purine pathways so that little is really known about purine transport in the gastrointestinal tract, or of changes in transport in states where purine metabolism is altered.

Indeed, at this time it is still not clear whether the gastrointestinal tract plays the role of purine absorber or secretor. It has been suggested that in man one-third of the uric acid eliminated is via the gastrointestinal secretions (Sorensen, 1960) so that the gastrointestinal tract can be considered an important 'extra-renal' route for the elimination of uric acid. On the other hand, Griebsch & Zollner (1974) showed the effect of dietary purines on plasma levels of uric acid to be much larger than had been expected and Peers (1977) concluded that when non-essential amino acid nitrogen is limiting, dietary RNA can provide a source of amino nitrogen.

The pancreas contains two enzymes capable of splitting nucleic acids, DNAase I (EC 3.1.21.1) and RNAase (EC 3.1.27.5). It is not clear whether the latter appears in pancreatic juice, but the DNAase is said to be present. Intraluminal flushings contain substances which can metabolize nucleic acid derivatives (Parsons & Shaw, 1983), although this ability could be derived from enzymes released into the lumen from shed cells. Whatever the source, the intestine will have a constant supply of uric acid from desquamated cells, the gastrointestinal secretions and the diet.

The effects that drugs normally used in the treatment of hyperuricaemia might have on transport is also unclear. Several reports have indicated that purine transport in the intestine may be altered in the presence of structurally related compounds (Schanker, Jeffrey & Tocco, 1963; Simmonds, Rising, Cadenhead, Hatfield, Jones & Cameron, 1973; Kolassa, Schutzenberger, Wiener & Turnheim, 1980; Shaw & Parsons, 1984*a*).

In this paper we report studies of the transport of uric acid in an *in vitro* recirculated segment of mouse small intestine and show for the first time that uric acid appears in the serosal secretions at a higher concentration than that in the lumen. This uptake is reduced in the presence of oxypurinol but, surprisingly, not by allopurinol or uracil. These results are discussed in relation to current views on intestinal transport of weak electrolytes and to the findings, many contradictory, of others.

METHODS

All reagents were of the highest purity available. The nucleic acid derivatives, allopurinol, oxypurinol and uricase (EC 1.7.3.3) were purchased from Sigma, [2-^{14}C]uric acid from Amersham International, NAD^+ and lactate dehydrogenase (EC 1.1.1.27) from Boehringer.

Animals

Adult male Balb C mice, bred in the Department of Biology, were kept in conditions of controlled daylight and temperature with free access to water and a stable laboratory diet (Oxoid modified Diet 4lb). Since seasonal variations occur in animals, wherever possible test and control experiments were intermingled with each other.

Analytical procedures

Glucose was assayed by commerical kit (COD-Perid, Boehringer) and lactate by a modification of the method of Leese & Bronk (1972), monitoring the reaction at 340 nm. Isotopic determinations were by liquid scintillation counting in Optiphase MP cocktail (LKB) using a LKB (Wallac) 2126 Rackbeta counter. Quench correction was by external channels ratio. ^{14}C counting was at 92% efficiency.

Chromatography

Samples were analysed by high performance liquid chromatography (h.p.l.c.) using an Altex 112 pump, 210 injection valve (fitted with a 20 μl loop) and a Beckman 165 variable wave-length detector.

Isocratic reverse phase chromatography with a 25 cm Hypersil 5 ODS analytical column (Anachem) fitted with a 5 cm guard column (dry packed with Lichropret (Anachem) in the laboratory) was used. Conditions of separation, the elution profiles, quantification and identification of the chromatographic peaks were as described by Shaw & Parsons (1984*a*).

In vitro perfusion

The method was essentially that of Morton & Hanson (1983), utilizing the recirculated 'segmented flow' technique of Fisher & Gardner (1974). Mice were anaesthetized (I.M.) with sodium pentobarbitone BP (140 mg kg wt.$^{-1}$, May and Baker Ltd.), a 16 cm segment of intestine (distal to the ligament of Treitz) was excised for the perfusion and suspended in liquid paraffin for the duration of the experiment.

The segment was initially recirculated with a modified glucose/bicarbonate-Ringer solution (Parsons & Volman-Mitchell, 1974) from one reservoir, which was then switched to a second reservoir at 15 min and recirculated for a further 85 min, time zero being the isolation of the segment of intestine. The solution in the second reservoir was identical with that in the first but also contained the substrate(s) to be followed.

The flow rate of the bicarbonate Ringer through the segment of intestine was 4 ml min^{-1} and mixed approximately 2:1 with bubbles of O_2/CO_2 (95/5%, v/v). The perfusate volumes were 100 ml, contained 28 mM-glucose, were continuously gassed with O_2/CO_2 and maintained at 37 °C. After an experiment the segment of intestine was cut open along its length, blotted, freed of any mesentery and dried to constant weight in an air oven (90 °C).

In routine experiments segments of intestine were recirculated with [^{14}C]uric acid at a specific activity of approximately 5×10^5 d.p.m. μmol^{-1}. This was increased 5-fold for the estimation of metabolism and tissue concentration.

Tissue concentration

(a) Segments of intestine were recirculated for 50 min as normal with the Ringer solution containing [^{14}C]uric acid, flushed through with ice-cold isotonic saline (9 g l^{-1}), cut open, blotted and the mucosal layer scraped off. A weighed sample of the mucosal scrape was suspended in 0·1 M-HNO_3 and extracted overnight at room temperature. After centrifugation aliquots of the supernatant were counted for ^{14}C. The total tissue water associated with each mucosal sample was determined by subtracting from the wet weight an estimate of the dry weight obtained from separate measurements of the ratio of dry weight to wet weight.

(b) Procedure as in (a) except that the mucosal scrape was frozen immediately in liquid nitrogen, denatured with trichloroacetic acid, neutralized with KOH and centrifuged at 3000 *g* through Centricon 30 filters (Amicon Ltd.). The final supernatant was diluted, with the mobile phase, and analysed by h.p.l.c. before and after incubation with uricase.

Expression of results

Results are expressed as concentrations or, where linear, as rates of appearance in the secretions on the serosal side of the preparation, per unit dry weight of intestine as determined by regression analysis. The uric acid content of mucosal tissue was expressed as concentration in the total tissue water.

Exogenous uric acid (that transported from the lumen) appearing in the serosal secretions is also expressed as the ratio of the concentration in the serosal fluid to that in the lumen.

Uric acid derived from the intestinal tissue is described as endogenous. Total uric acid concentrations in tissue and serosal secretions are the summation of the endogenous and exogenous concentrations.

The contribution of exogenous uric acid to the total serosal uric acid is calculated from the ratio of the specific radioactivities (^{14}C) of uric acid in the serosal fluid and the luminal solution, and expressed as %.

Values are means ± S.E. of the mean (for n determinations), and statistical comparisons are by Student's t test.

RESULTS

Metabolism of uric acid

Duplicate analyses of [2-^{14}C]uric acid by h.p.l.c. showed 98·4 % of the radioactive counts to be associated with the uric acid peak. After recirculating a segment of intestine for 85 min, 99·3 % of the counts in the serosal secretions were associated with the uric acid peak, demonstrating that uric acid metabolism by the small intestine was negligible over the experimental period.

Serosal glucose and lactate

The serosal appearance of glucose (47·2 ± 3·3 μmol min^{-1} g dry wt.$^{-1}$ (8)) and lactate (20·1 ± 1·5 (7) μmol min^{-1} g dry wt.$^{-1}$) was linear over the experimental period with slight falling off after 90 min. The glucose concentration in the luminal fluid at the end of the experiment had fallen from 28 to 24·2 ± 0·2 mM (22).

The mean serosal fluid concentrations over the experimental period 20–100 min for glucose and lactate were 86·6 ± 1·0 mM (101 determinations from 17 experiments) and 35·6 ± 1·0 mM (51 determinations from 8 experiments) respectively.

There were no significant differences between the controls and any of the experimental groups reported in this paper with respect to the rate of appearance of serosal glucose or lactate (all $P > 0·1$).

Serosal fluid

There were no significant differences in the rate of appearance of serosal fluid in any experimental group when compared with control values (0·47 ± 0·02 ml min^{-1} g dry wt.$^{-1}$ (8)) or each other (all $P > 0·1$).

Components of the serosal secretions

When the serosal secretions were analysed by h.p.l.c. three endogenously derived substances were detected. Two were identified as uric acid and uracil from spectral, chromatographic and, in the case of uric acid, enzymatic analysis (see Methods). The third component had a U.V. spectrum, characteristic of a nucleic acid derivative, and an elution pattern similar to that of a nucleoside under different chromatographic conditions.

Serosal uric acid

Exogenous. The serosal appearance of exogenous uric acid (i.e. that transported from the lumen) was linear over the experimental period and directly proportional to the luminal concentration, over the range studied (Table 1). The rate of serosal

appearance of uric acid in the presence of 0·1 mM-uric acid and 0·3 mM-allopurinol or 0·3 mM-uracil was not significantly different ($P > 0·1$ for both) from the rate (60 ± 3 nmol min^{-1} g dry $wt.^{-1}$ (9)) with only uric acid present in the lumen. However, the transport was significantly ($P < 0·05$) reduced to 51 ± 3 nmol min^{-1} g dry $wt.^{-1}$ (7) when 0·3 mM-oxypurinol was present (Table 1).

TABLE 1. Appearance of uric acid in serosal secretions of mouse small intestine in the absence and presence of oxypurinol, allopurinol or uracil

	Lumen		Serosal uric acid		
				Total uric acid concentration exogenous + endogenous (μM)	
n	Uric acid (μM)	Addition	Rate of appearance of exogenous uric acid (nmol min^{-1} g dry $wt.^{-1}$)	at 50 min	at 100 min
4	12·2 ± 0·3	None	8·5 ± 0·3	68 ± 4	44 ± 4
5	54·0 ± 2·0	None	30·0 ± 3·0	127 ± 5	97 ± 3
9	106·0 ± 3·0	None	60·0 ± 3·0	191 ± 6	163 ± 4
7	105·0 ± 3·0	Oxypurinol	51·0 ± 3·0	128 ± 5	123 ± 4
7	103·0 ± 3·0	Allopurinol	60·0 ± 3·0	133 ± 4	127 ± 4
7	105·0 ± 6·0	Uracil	61·1 ± 4·0	191 ± 5	152 ± 6
4	0	None	—	58 ± 5	36 ± 4

Values are means ± S.E. of means (of *n* animals). Where present the concentrations of oxypurinol, aliopurinol and uracil were 296 ± 8, 300 ± 2 and 295 ± 8 μM, respectively.

Table 2 gives the ratios of exogenous uric acid concentration in the serosal secretions to that in the luminal fluid (SF/LF). It can clearly be seen that with uric acid alone in the lumen this ratio is approximately 1·18 regardless of the concentration of uric acid in the lumen. With 0·1 mM-uric acid and 0·3 mM-oxypurinol in the lumen (Table 2) the ratio is significantly reduced (all $P < 0·05$) to approximately 1·06. When 0·1 mM-uric acid and 0·3 mM-allopurinol (7) or 0·3 mM-uracil (7) were present in the lumen the SF/LF concentration ratios were not different ($P > 0·1$ for all values over the experimental period for both additions) from the values with uric acid alone in the lumen.

Total. The total uric acid appearing in the serosal secretions is composed of an exogenous and an endogenous component. With 0·1 mM-uric acid in the lumen the total concentration in the serosal fluid sample at 50 min was greater than that at 100 min (Table 1). This indicates that the endogenous uric acid washing out of the intestine decreases throughout the experiment, since the serosal appearance of exogenous uric acid is linear. This was confirmed with experiments where no uric acid was present in the lumen (Table 1), which also showed that exogenous uric acid in the lumen did not affect the serosal appearance of endogenous uric acid.

These data also reveal that uric acid is transported from the lumen against a high 'apparent' concentration gradient when considering the total uric acid present in the serosal secretions. For instance, in the case of 12·2 μM-uric acid in the lumen this ratio is about 5·6 after recirculating for 50 min (Table 1).

The total serosal uric acid concentrations with 0·1 mM-uric acid and 0·3 mM-uracil

compare well with the values obtained with only 0·1 mM-uric acid in the luminal solution. When the serosal appearance of endogenous uric acid with no luminal uric acid was compared with that in experiments with 301 ± 5 (4) μM-uracil alone in the lumen there were no significant differences (all $P > 0{\cdot}1$ except for the serosal fluid sample at 90 min where $P > 0{\cdot}05$) over the whole experimental period. This suggests that uracil has no effect on the production and serosal appearance of endogenous uric acid.

TABLE 2. Time dependence of SF/LF concentration ratios for exogenous uric acid (serosal uric acid/ luminal uric acid)

	Exogenous uric acid SF/LF concentration ratio			
Time of perfusion (min)	$12{\cdot}2 \pm 0{\cdot}03$ μM-luminal uric acid ($n = 4$)	54 ± 2 μM-luminal uric acid ($n = 5$)	106 ± 3 μM-luminal uric acid ($n = 9$)	105 ± 3 μM-uric acid + 296 ± 8 μM-oxypurinol ($n = 7$)
20	$0{\cdot}19 \pm 0{\cdot}01$	$0{\cdot}15 \pm 0{\cdot}02$	$0{\cdot}14 \pm 0{\cdot}02$	$0{\cdot}11 \pm 0{\cdot}02$
30	$0{\cdot}90 \pm 0{\cdot}03$	$0{\cdot}83 \pm 0{\cdot}02$	$0{\cdot}85 \pm 0{\cdot}03$	$0{\cdot}73 \pm 0{\cdot}04$
40	$1{\cdot}11 \pm 0{\cdot}04$	$1{\cdot}15 \pm 0{\cdot}02$	$1{\cdot}15 \pm 0{\cdot}02$	$1{\cdot}00 \pm 0{\cdot}03$
50	$1{\cdot}18 \pm 0{\cdot}01$	$1{\cdot}18 \pm 0{\cdot}03$	$1{\cdot}18 \pm 0{\cdot}02$	$1{\cdot}08 \pm 0{\cdot}03$
100	$1{\cdot}15 \pm 0{\cdot}02$	$1{\cdot}16 \pm 0{\cdot}02$	$1{\cdot}17 \pm 0{\cdot}01$	$1{\cdot}06 \pm 0{\cdot}03$

Values are means $\pm$ S.E. of means (of n animals).

When the specific activity of serosal [^{14}C]uric acid was followed with 0·1 mM-uric acid in the lumen, 76 ± 2 (9) % of the total serosal uric acid was exogenous, i.e. transported from the lumen. With 0·1 mM-uric acid and 0·3 mM-allopurinol or 0·3 mM-oxypurinol present in the lumen, 96 ± 2 % (7) and 92 ± 2 % (7) was respectively exogenous. With 0·1 mM-uric acid and 0·3 mM-uracil this value was 79 ± 3 % (7), not significantly different ($P > 0{\cdot}1$) from the value with uric acid alone in the lumen.

These data suggest that the endogenous sources of uric acid must be almost totally derived from the catabolism of nucleic acid derivatives via xanthine oxidase (rather than from some intracellular store of uric acid), and therefore they must originate in the epithelial cells. Obviously uracil does not affect this enzyme or the production and serosal secretion of endogenous uric acid.

Table 3 shows the profile of concentrations across the *in vitro* preparation. With 105 μM-uric acid in the lumen (A in Table 3) the concentration of exogenous uric acid is 47 μM in the mucosa and 122 μM in the serosal secretions, giving a SF/LF concentration ratio of $1{\cdot}16 \pm 0{\cdot}01$ (6). In fact the uric acid is actually transported into a much higher concentration (205 μM) if the total serosal uric acid is considered. Even when the exogenous uric acid in the mucosa (47 μM) is compared with that in the serosa (122 μM) transport appears to be against a large gradient.

With 87 μM-uric acid in the lumen (B and C in Table 3) the total uric acid concentrations are 105 μM (2) in the mucosa and 165 μM (2) in the serosal secretions. The exogenous SF/LF uric acid concentration ratio is 1·17 (2). Again transport is against a larger gradient when the total serosal uric acid is considered. It is worth stressing that although the mucosal concentration of exogenous uric acid is less than

that in the lumen, the total mucosal concentration is in fact higher. However, the total uric acid concentration in the tissue (105 μM) is considerably lower than that in the serosal secretions (165 μM).

TABLE 3. Uric acid concentrations after recirculation through mouse small intestine for 50 min

Expt.	Lumen (μM)	Mucosal tissue (μM)	Serosal secretions (μM)		
			Exogenous	Endogenous	Total
A	105±2	47±2	122±2	83±4	205±5
B	87	107	103	60	163
C	86	102	100	66	166

For experiment A values are means±S.E. of means for six experiments with [^{14}C]uric acid, and the mucosal uric acid is only exogenous. B and C are individual experiments in which the mucosal uric acid was determined by h.p.l.c., and is the total of endogenous and exogenous concentrations.

Allopurinol and oxypurinol

In the experiments with 300 μM-allopurinol and uric acid present in the lumen (Table 1) the serosal appearance of allopurinol (55±3 nmol min^{-1} g dry wt.$^{-1}$ (7)) was linear and it reached a concentration of 122±5 μM (7). Strangely, only a very small amount of oxypurinol (its metabolite) was seen in the serosal secretions (two experiments had no detectable serosal oxypurinol). The highest concentration seen was 7 μM. However, a new, unidentified peak appeared in quite large amounts on the chromatogram of serosal fluid collected from these experiments. The new peak had a retention time of 20 min, clearly distinguishing it from allopurinol (18 min), oxypurinol (16 min) or uric acid (10·7 min), although its U.V. spectrum was similar to that of allopurinol with λ_{max} at 255 nm and a small trough at 235 nm.

With oxypurinol (296 μM) and uric acid present in the luminal solution, oxypurinol appeared in the serosal fluid at a linear rate (91±5 nmol min^{-1} g dry wt.$^{-1}$ (7)) and reached a concentration of 188±8 μM (7).

In both sets of experiments with allopurinol or oxypurinol present in the lumen both hypoxanthine and xanthine appeared in the serosal secretions.

Uracil

In the experiments with uric acid and 295 μM-uracil present in the lumen the rate of serosal appearance of uracil was 137±4 nmol min^{-1} g dry wt.$^{-1}$ (7) and linear. In experiments with uracil (301±5 μM (4)) present alone in the lumen the rate of serosal appearance was 136±5 nmol min^{-1} g dry wt.$^{-1}$ (4). There were no significant differences (all $P > 0{\cdot}1$) between the serosal concentration of uracil in the presence and absence of uric acid over the time course of the experiments. The highest concentration measured in the serosal secretions over the experimental period was 276±8 μM (7). Since the endogenous uracil washing out of the intestine into the serosal secretions was negligible after 40 min this did not contribute significantly to the total uracil measured during the remainder of the experimental period.

DISCUSSION

A serosal concentration of 86 mM-glucose with 28 mM present in the lumen indicates active transport of this sugar by loops of mouse intestine, and the low production of serosal lactate (under half that of serosal glucose) suggests good oxygenation of the preparation. These characteristics indicate that isolated loops of mouse intestine can provide a useful preparation for studying transport. The data for glucose transport and fluid secretion compare well with those of Morton & Hanson (1983, 1984) obtained with 10-week-old lean mice. Their glucose uptake, approximately 30 μmol min^{-1} g dry wt.$^{-1}$ and fluid secretion, 0·33 ml min^{-1} g dry wt.$^{-1}$ are lower than the values in the present study, but this is to be expected, since they used the whole small intestine whereas in the present study only jejunum was used.

The results presented in this study clearly show that, *in vitro*, the small intestine of mouse is capable of transporting uric acid from the lumen to the serosal side of the preparation. The experiments involving [^{14}C]uric acid and incubations with uricase confirm that there is no metabolism of the substrate by the intestine during the course of an experiment. Thus, when the SF/LF concentration ratio of exogenous uric acid was found to be greater than 1, there was no contribution from a metabolite. What is interesting is that this ratio (1·18) remains constant over the luminal concentration range (approximately 0·1–0·01 mM) studied.

It has been reported that the intestinal transport of uric acid is passive (see, for example, Khan, Wilson & Crawhall, 1975) and probably occurs by non-ionic diffusion since it has been shown that the small intestine is most readily penetrated by the non-ionized form of weak acids (Schanker, Tocco, Brodie & Hogben, 1958). However, uric acid, a weak acid, will exist almost exclusively as the monovalent anion at physiological pH (Bergmann & Dikstein, 1955).

It has been suggested that the transmural pH and electrical gradients alone cannot account for the mechanism of intestinal transport of weak electrolytes, although a proposed three-compartment model, with an intermediate compartment of high pH, would do so (Jackson, Shiau, Bane & Fox, 1974). However, this proposal has since been modified several times (see, for example, Jackson, 1977; Jackson, Tai & Steane, 1981; Tai & Jackson, 1981). The electrical potential across the small intestine is in the range 5–10 mV, with the serosa positive, and is dependent upon the activity of the sodium pump (Clarkson, Cross & Toole, 1961). This would favour the movement of negatively charged species, from mucosa to serosa. Since uric acid is predominately negatively charged in the region of pH 6·0 (the suggested pH at the luminal surface, Lucas, 1983) or above, it is possible that its movement is influenced by the transmural p.d. or more likely by the larger p.d. across the basolateral membrane. Fluid absorption may also introduce additional factors such as solvent drag.

Whatever the mechanism(s) involved in the movement of uric acid the exogenous SF/LF concentration ratio is significantly greater than one, and the concentration of exogenous uric acid in the mucosa is below that in the lumen. This implies that the accumulation is not at the brush-border membrane. Brush-border membrane vesicle studies with uric acid indicated no ion-stimulated 'overshoot' phenomena (Shaw & Parsons, 1984*b*) or 'competition' for uptake by related compounds (Shaw

& Parsons, 1985) in the mouse, supporting the idea that there is no specific mechanism at the luminal surface.

Studies with rings of mouse small intestine (Shaw & Parsons, 1985) gave lower exogenous uric acid tissue concentrations than those in the medium after 10 min incubations. Taken with the present data this suggests that it is not the brush-border membrane which has the ability to establish and maintain a SF/LF concentration ratio of exogenous uric acid greater than 1.

However, the present study is further complicated because the total concentration (endogenous and exogenous) of uric acid in the mucosa was above that in the lumen, so that it does appear that uric acid can move against a concentration gradient at the brush border. In the absence of exogenous uric acid there is no evidence for secretion into the lumen, and the presence of exogenous uric acid does not affect the appearance of endogenous uric acid in the serosal secretions.

What these results do not explain is whether the uric acid in the tissue exists as a single pool or two independent pools draining into the serosal fluid. This question requires further attention, but it is clear that there is a gradient against transport into the serosal secretions when considering both the exogenous and total uric acid concentrations.

It is interesting to note that the transport of exogenous uric acid is not affected by the size of the endogenous pool of uric acid. In the presence of allopurinol the production of endogenous uric acid was negligible but the transport of exogenous uric acid was unaffected.

The presence of oxypurinol in the lumen decreased the serosal appearance of exogenous uric acid, but the presence of uracil did not. The failure of allopurinol to affect the movement of uric acid is at variance with several reports in the literature in which it has been shown to reduce the secretion of hypoxanthine in guinea-pig intestine (Kolassa *et al.* 1980), to decrease the uptake of guanine in pig intestine (Simmonds *et al.* 1973) and uric acid in rat intestine (Shaw & Parsons, 1984*a*).

The present data are also at odds with a recent report (Shaw & Parsons, 1985) which shows a reduction in uric acid uptake in the presence of allopurinol, using *in vitro* preparations of rings cut from mouse intestine.

One possible explanation of this anomaly is that it is the metabolite, oxypurinol, which is responsible for any alteration in purine movement. The capacity of mouse intestine to metabolize allopurinol was small since very little oxypurinol was detected. The incubation media in the tissue ring experiments did not contain glucose, since only short time course experiments were performed, and it might be expected that fluid transport would be less than that in the present study, where glucose is present. It is possible that in the present study fluid transport influenced the tissue concentrations of allopurinol, and therefore the oxypurinol derived from it, to such a degree that the tissue oxypurinol was never high enough to affect uric acid movement.

If the allopurinol was rapidly washed out of the segment of intestine, this would explain why little or no oxypurinol was detected in the serosal secretions, and perhaps also explain why uracil reduced uric acid uptake in tissue rings (Shaw & Parsons, 1985) but not in this study.

This anomaly could also be explained if high fluid or glucose transport resulted in a greater proportion of the substances moving to the serosa by the paracellular route. This would obviously reduce or negate any effects that needed cellular transport.

The implication from the above suggestions is that the uptake and transport of these compounds is particularly sensitive to fluid transport.

This might help explain the secretion of hypoxanthine seen by Kolassa *et al.* (1980) since under certain conditions it is possible for the intestine of the guinea-pig to secrete rather than absorb fluid. The only other report of secretion of purines is in hamster intestine (Berlin & Hawkins, 1968). Interestingly hamster produces an alkaline secretion, i.e. bicarbonate is secreted into the lumen, whereas the upper intestine of most species produces an acid secretion (Wilson & Kazyak, 1957).

It has previously been reported that thymine and uracil interfere with the intestinal absorption of the purines, leading to the suggestion that there is a common transport system for the pyrimidines and the purines (Schanker *et al.* 1963). The present results do not support this since uracil did not influence uric acid transport or vice versa. Interestingly uracil also had no effect on the production and serosal appearance of endogenous uric acid. It could be argued that any effects allopurinol and oxypurinol have in the intestine are mediated through metabolism, which seems unlikely for uracil.

In conclusion, it can be said that the transport of uric acid in the intestine of the mouse is complicated and may be influenced by several factors. Further research is needed into the role which fluid movement across the intestine may play, since this may well explain some of the anomalies that have arisen.

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