

Intestinal absorptive function

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Abstract

The normal gut is adapted to intermittent feeding with complex macromolecular substrates of low sodium content. The high permeability of the upper small intestine to sodium, together with sodium rich saliva and pancreaticobiliary secretions results in large sodium fluxes into the lumen. These substantial sodium influxes are matched by equally large effluxes from the ileum and proximal colon, which are comparatively impermeable to sodium and capable of active sodium absorption. Resection of these distal, sodium absorbing regions of the intestine, lead to problems with sodium depletion. Controlled transit of chyme is essential to permit time for optimum digestion and absorption and a range of feedback control mechanisms exist. Partially digested nutrients, both in the duodenum and ileum, exert inhibitory feedback to delay delivery of further nutrients and here again surgery may compromise these reflexes. Brush border hydrolase values are strongly influenced by luminal nutrient concentrations, being impaired by malnutrition and total parenteral nutrition, but restored by enteral feeding. Viscous fibre slows absorption and may delay transit through mechanisms that are as yet uncertain. Whether and how novel substrates activate normal control mechanisms will be important factors determining their effectiveness and patient acceptability.

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Absorption in its most restricted sense consists of the process whereby nutrients pass from the gut lumen either across the brush border cell membrane after binding to a specific transport protein, or through the intercellular tight junction, in effect crossing the barrier between the external milieu and the organism. This process requires a very extensive 'preprocessing' of food to permit the intimate contact between substrate and enterocyte needed to permit the binding of nutrient to the various transport proteins.

Preprocessing of food before absorption

Food is usually composed of macromolecules, often part of other organisms and hence has complex structures such as cell walls that require breaking down before the nutrients can be accessed. This is best illustrated by considering the digestion of starch. Mechanical and chemical degradation begins with cooking, which hydrates the long starch polymers

causing them to lose some of their ordered array permitting better access of salivary amylase.¹ Grinding by the teeth and later by the action of the 'antral pump', combined with the action of salivary amylase, reduces the food to an homogenous chyme, which is pumped into the duodenum at a rate of about 1-2 kcal/min. Once within the duodenum, starch is hydrolysed extremely rapidly because of a superabundance of pancreatic amylase, which cleaves the α 1-4 glucosidic bonds in starch, reducing the polymer to maltose, maltotriose, and α limit dextrans. Attached to the brush border, facing into the gut lumen are the brush border hydrolases, large glycoproteins now sequenced, which include maltase, isomaltase-sucrase, and glucosidases capable of reducing α limit dextrans and other polymers containing less than six glucose monomers, to glucose monomer. This then binds to the glucose/sodium cotransporter, a 72 kilo dalton protein, whose affinity for glucose is appreciably increased when it combines with sodium. Depending upon exactly where in the body the cell membrane is derived, either one or two sodium molecules bind to the transport protein. This then undergoes conformational change, which transports the glucose and sodium across the cell membrane to be released into the cytoplasm.² In effect this system uses the chemical gradient of sodium across the enterocyte brush border membrane, generated by the 'pumping' action of the basolateral Na^+/K^+ ATPase, to energise active glucose transport.

Delivery of nutrients to the small intestine

Emptying of gastric chyme is to a considerable extent controlled by feedback inhibition, whereby nutrients and hyperosmolar solutions within the duodenum inhibit antral peristalsis and reduce fundal tone, causing food to be redistributed more proximally within the stomach. This 'duodenal brake' is the first of many such control loops whereby the arrival of excess nutrients distally delays further delivery, hence permitting more time for digestion and absorption. Such feedback loops are vital because of the very variable nutrient content and digestibility of food. Detectors positioned distally can assess how successful digestion has been and moderate the flow of chyme to minimise malabsorption. The best example of what happens if these feedback loops are lost is the malabsorption that commonly accompanies the precipitous and uncontrolled gastric emptying seen in patients with the 'dumping syndrome' after vagotomy and pyloroplasty, or to a lesser degree in most patients with a gastroenterostomy.

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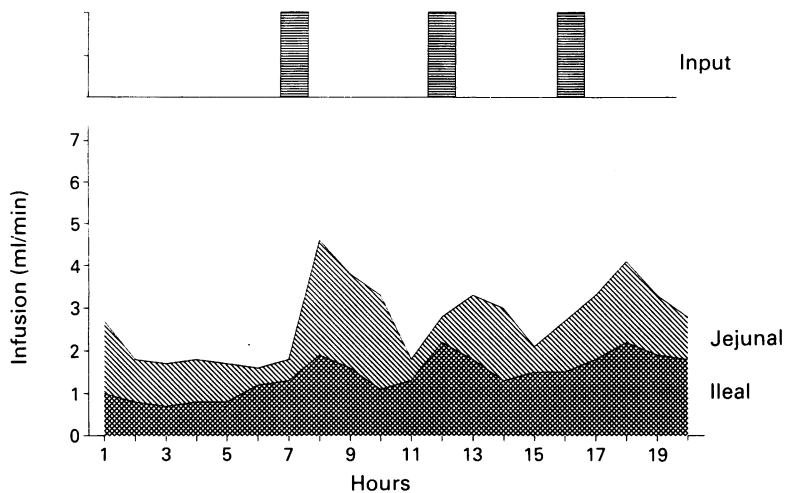


Figure 1: Flow through the upper gastrointestinal tract studied over 20 hours by means of a slow marker infusion technique combined with aspiration from the upper jejunum and distal ileum.⁴

Enteral nutrition to a large extent avoids such problems by in effect doing most of the mechanical and chemical preprocessing for the patient. Thus commercial enteral diets are homogenised, isotonic, and often partially digested. Furthermore by using a pump to deliver nutrients at 1 cal/min problems with abnormal gastric emptying can be avoided except in exceptional cases such as severe head injury, when gastric stasis can be profound.³

Intestinal absorption

Before considering absorption from enteral diets it is worth considering the normal response to feeding as these are the conditions that the gut has evolved to cope with. Figure 1 shows that although input into the organism is pulsatile, the stomach reduces this very considerably so that the fluctuation in flow is less in the jejunum, and the ileum is exposed to still smaller variations.⁴ In general there are important differences between the jejunum, which is exposed to high flow and high concentrations of nutrients compared with the ileum, which receives a smaller load and must absorb from lower concentrations. These differences in load result in quite considerable regional differences in absorptive characteristics as is clearly seen with sodium absorption.

SODIUM ABSORPTION

Most of our food has a low sodium concentration comparative with blood. A normal beefburger meal, if homogenised, has a sodium concentration of only 35 mmol. Sodium rich saliva raises this somewhat but in the stomach acid secretion lowers the sodium content still further. The duodenum is therefore exposed to a sodium concentration of 20–30 mmol. The jejunum cannot, however, maintain such a gradient being highly permeable to sodium, which is rapidly secreted into the gut lumen.⁵ This secretion, combined with the very rapid simultaneous absorption of water, means that, by the time the chyme reaches the ileum, the sodium concentration has reached 120 mmol. The ileum receives approximately 400 mmol of

sodium per 24 hours, which it reduces to about 200,^{4,6} the colon absorbing 95% of this to result in stool output of 10–20 mmol/24 h. The ileum is adapted to absorbing sodium against its electrochemical gradient and this requires that the ileum be impermeable to sodium. It is, however, more permeable to chloride ions and so does not generate much of a lumen-serosa potential difference when exposed to an isotonic salt solution. By contrast the colon is highly impermeable to both sodium and chloride and generates a high electrochemical gradient by active electrogenic sodium transport, lowering the luminal sodium concentration to 20–30 mmol and the luminal-serosa potential difference to -35 mV.⁷

SIGNIFICANCE OF REGIONAL DIFFERENCES IN ABSORPTION

These differences become of great importance when the functions of various regions of the gut are lost by disease or surgical resection. Ileal resection results in a doubling of the sodium load to the colon, although this can usually be compensated for by increased colonic absorption,⁸ stool output does increase in most cases.⁹ The major problem is when the colon is also resected when the vast sodium flow from the jejunum becomes stoma effluent. This point is well made by the studies on the short bowel patients (Fig 2). Patients with less than 100 cm of jejunum remaining could not absorb sufficient salt to avoid desalination and were dependent on daily intravenous saline.¹⁰ In these patients salt balance is highly precarious but vital to control. The situation can be much improved by careful choice of fluids

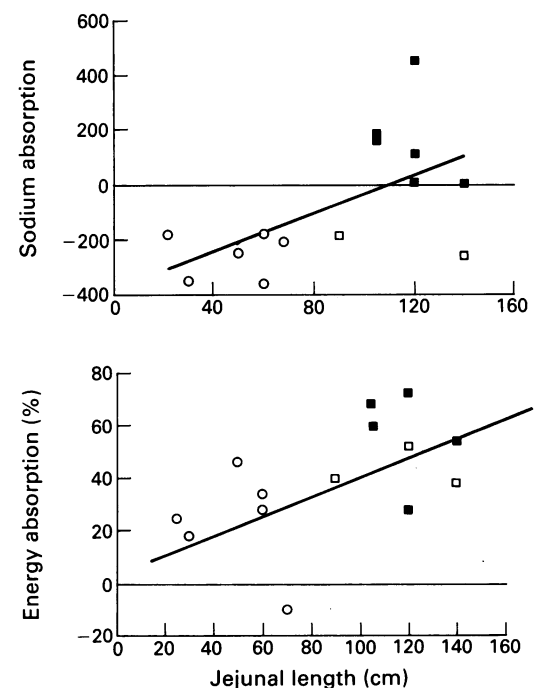


Figure 2: Influence of jejunal length on salt and energy balance in patients with jejunostomy. Fourteen patients with extensive small bowel resection and a high jejunostomy and one patient with a jejunorectal anastomosis had balance studies. No patient with less than 100 cm of jejunum could maintain a positive sodium balance by the enteral route alone.¹⁰

once the implications of the high jejunal permeability to sodium are appreciated. Drinking low sodium fluids such as water causes massive sodium secretion and hence negative balance whereas the use of high sodium drinks minimises the negative balance. There is a linear relation between sodium concentration and sodium absorption from nutrient solutions (Fig 3). Net absorption only occurs from saline, non-nutrient solutions perfused into the jejunum if the sodium concentration exceeds 127 mmol,⁵ whereas net absorption occurs from nutrient solutions with sodium concentrations greater than 90 mmol,¹¹ this enhancement is a result of the cotransport of sodium and glucose. Thus optimum sodium balance can be achieved by the use of fluids containing 90 mmol sodium together with nutrients such as starch or amino acids, similar to the solutions used so successfully in the treatment of cholera.

NUTRIENT ABSORPTION

There are important differences for nutrients (as for sodium) between the jejunum, which is exposed to high loads of nutrients at high concentrations (Table I),¹² and the ileum, which must absorb small amounts of nutrients from a low concentration,¹³⁻¹⁵ generating high concentration gradients. These differences in

TABLE II Flow and motility during continuous enteral nutrition. Six subjects were intubated and terminal ileal flow assessed using a slow marker infusion technique for five hours fasting and during five hours of continuous enteral feeding with 1 kcal/min of a mixed nutrient polymeric diet. While intraduodenal feeding abolished fasting activity intragastric feeding did not. (Data from reference¹⁸)

		Intragastric	Intraduodenal
Terminal ileal flow (ml/min)	Fasting	0.3 (0.1)	0.6 (0.3)
	Fed	0.4 (0.1)	2.0 (0.7)*
Motility MMC/5 h	Fasting	7.2 (1.8)	7.8 (2.8)
	Fed	11.1 (2.4)	Absent

Data expressed as mean (SEM); * $p < 0.05$.

operating conditions are reflected in differences in transport processes. Thus in the rat two distinct transport processes for glucose have been shown. One, which predominates proximally, is characterised by a high V_{max} and K_m , ideal for transporting large amounts of glucose from solutions of high concentration, while the other, which predominates in the ileum¹⁶ has a low V_{max} and K_m , well suited for transport of smaller loads from solutions of a much lower concentration. The renal glucose/sodium transporter likewise has two forms, one in the proximal convoluted tubule with a high V_{max} and K_m , and another in the distal tubule, which is exposed to much lower glucose concentrations with a low V_{max} and low K_m . This more distal transporter generates a much bigger concentration gradient and requires the cotransport of two sodium molecules/glucose molecule instead of the one that suffices in the proximal tubule. Thus the energy for transport ultimately derives from the Na^+/K^+ ATPase pump, which generates the lumen-cytoplasmic sodium gradient.

Importance of motility for absorption

Efficient absorption is dependent on adequate mixing both to permit breakdown of food to a homogenous chyme and also to permit close contact between nutrients and their transport proteins lying in the brush border membrane. The entry of nutrients into the duodenum after a normal meal causes a radical change in motility patterns, the normal cyclical fasting activity, the 'migrating motor complex', being replaced by irregular fed activity designed to mix the chyme and, by constantly 'kneading' it, pushing the absorptive surface into the chyme and so speeding up absorption. The precise pattern of the mixing activity is influenced by the nature of the nutrient, glucose producing the least activity while fat induces the most contractions, all of which are non-propulsive.¹⁷

The switch from fasting to fed activity requires a minimum amount of calories, probably about 1-2 kcal/min. This is the value of calorie load that enteral diets provide and a recent study¹⁸ from Central Middlesex Hospital (Table II) has shown that while intraduodenal infusion at 1 kcal/min does abolish fasting activity, intragastric infusion at the same rate does not. This shows that it is the intraduodenal concentration that is critical, rather than the precise load. Delivery into the

TABLE I Postprandial nutrient luminal concentrations of carbohydrate, protein, and fat (combined data from references¹²⁻¹⁵)

	Carbohydrate		Protein		Fat	
	g/l	Free glucose (mM)	g/l	Oligopeptide (mM)	g/l	FFA (mM)
Jejunum	5-50	30-250	10-30	20-150	10-15	2-20
Ileum	1-3	5-20	1-2	20-80	3-6	1-6

FFA=free fatty acid.

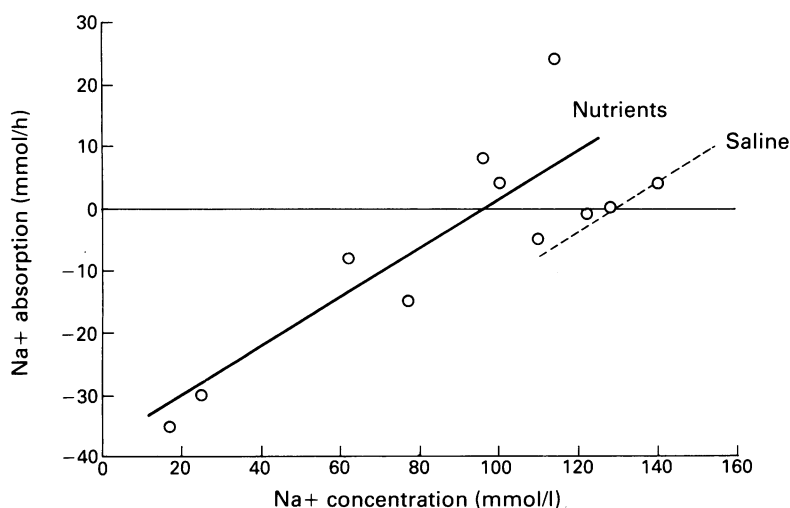


Figure 3: Correlation between Na^+ concentration and nutrient absorption. Sodium absorption from a 25 cm jejunal segment was assessed using a jejunal perfusion technique. Isotonic nutrient solutions made up of partially hydrolysed starch and free amino acids with varying sodium concentrations were studied each in seven subjects. Sodium absorption was strongly correlated ($r = 0.95$, $p < 0.001$) with initial sodium concentration.¹¹ The dotted line shows the relation between sodium absorption and infused concentration for a non-nutrient, saline/mannitol solution⁵ illustrating the enhancement of sodium absorption in the presence of nutrients.

stomach presumably causes sufficient dilution of feed by gastric juice so that the intraduodenal concentrations fail to reach the level for switching off fasting activity. This does not, however, seem to impair absorption, because in the same study colonic inflow did not rise above fasting concentrations. This probably reflects the fact that in humans migrating motor complexes rarely pass the whole way down the small intestine, most fading out in the distal ileum. Indeed slow continuous feeding by the nasogastric route probably improves absorption by avoiding the surges in flow characteristic of normal episodic feeding. Thus when normal diets have been compared with similar amounts of calories fed nasogastrically by continuous infusion the faecal or stomal losses have been shown to be significantly less.¹⁹ This is of great significance in the early nutritional rehabilitation phase after bowel resection.

In addition to the feedback inhibition from nutrients in the duodenum on gastric emptying there are more distal sensors especially in the ileum of both humans^{20 21} and laboratory animals,^{22 23} which detect malabsorbed nutrients, especially fat, and exert an inhibitory effect not only on gastric emptying²⁴ but also on duodenal and jejunal motility, delaying transit.^{20 25} This results in increasing the time available for absorption. This has been shown to increase the completeness of absorption, at least for carbohydrate in normal subjects.²⁶

These early studies on this phenomenon, 'the ileal brake' were performed by infusing nutrients directly into the ileum. There are of course other ways in which malabsorption can be mimicked. Amylase inhibitors delay starch digestion and were used by Layer *et al*²⁷ to increase the amount of glucose in the distal ileum. Their study showed that impairing starch digestion caused an early inflow of starch into the ileum, ileal flow then levelled off as a considerable inhibition of gastric emptying then ensued. This shows how the ileal brake can act to compensate for defects in the absorptive apparatus.

Similar reflexes are probably activated when various viscous fibres are added to enteral diets. Thus it is known that guar delays absorption of glucose by a combination of delaying gastric emptying and more importantly delaying the absorption from the lumen of the small intestine.²⁸ Similar studies by Jenkins *et al*²⁹ showed that the delay in glucose absorption did not interfere with overall absorption so that although absorption of xylose was reduced at two hours, by eight hours total absorption was unchanged. Although the fibre added to enteral feeds cannot be very viscous without blocking the feeding tube, the fibre that has been used can be shown to reduce the area under the concentration time curve for both folic acid and zinc during the first few hours, as well as delaying mouth to caecum transit.³⁰ Thus nutrients are probably retained from longer in the gut lumen and pass further down the gut, activating compensatory reflexes, which delay transit and permit more time for absorption.

EFFECT OF MALNUTRITION AND STARVATION ON EFFICIENCY OF ABSORPTION

Patients fed by enteral nutrition have often had a previous period of starvation or total parenteral nutrition during which luminal nutrient concentrations will have been very much reduced. This has been clearly shown to reduce brush border hydrolase concentrations without changing the jejunal morphology in humans,³¹ and in smaller laboratory animals to reduce mucosal mass. In vitro studies³² have furthermore shown that the number of glucose cotransporters could be increased in this situation by infusing nutrients into the jejunum. Fortunately the impairment of absorption caused by luminal deprivation of nutrients is rapidly (15–24 hours) corrected by refeeding enterally.

Absorption is normally highly efficient, both for water and electrolytes as well as for nutrients. This efficiency depends on many adaptive responses, which occur within very different time scales. Control of the transit of chyme down the gut depends on negative feedback inhibition of transit by malabsorbed nutrients reaching more distal parts.^{20 21 24 25} changes that occur within a few minutes. Over several hours or days changes in luminal nutrient concentration also lead to adaptive changes in brush border hydrolases and transport proteins,^{31 32} while longer periods are associated with morphological changes. Luminal nutrients are vital to maintain efficient absorption, a fact that should encourage the use of the enteral nutrition as soon as is possible.

Novel substrates will need to be assessed carefully to ensure that they stimulate the appropriate gut receptors and elicit responses that permit controlled transit down the gut. Sucrose polyester, a synthetic fat substitute, was an interesting example of a novel, non-nutritive substance which, although it tasted like fat, did not activate the 'duodenal brake' and actually emptied from the stomach like water.³³ Care will be needed to ensure that the controls on motility operate normally in the presence of novel nutrients if their use is not to be marred by precipitous transit through the gut.

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