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The chemistry of aluminium in the gastrointestinal lumen and its uptake and absorption

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A large number of experimental studies have been carried out on the intestinal absorption and/or uptake of Al, and on the factors that affect this. However, apart from the well-known problems of contamination and the difficulty of analysis of Al, many of these studies have been flawed, particularly when experimental solutions have been used, since often it has not been realized that the Al has precipitated at physiological pH. Other problems have included inappropriate use of buffers (such as containing phosphate) and extrapolation of results from unphysiologically high levels to dietary levels.

Here we shall assess the chemistry, uptake and absorption of Al from the gastrointestinal tract, and in particular consider the importance of dietary, rather than pharmacological, levels to which the general population is exposed.

CHEMISTRY OF ALUMINIUM IN THE GASTROINTESTINAL TRACT

There are few reports of the fate of Al along the lumen of the gastrointestinal tract other than that Al is very poorly absorbed and its absorption can be interfered with by dietary cofactors. Present theory (Stewart, 1989; Lote & Saunders, 1991) suggests that most ingested forms of Al are at least gradually soluble in acid, so some Al will be solubilized in the chlorhydric stomach after ingestion. When stomach contents reach the duodenum they would be rapidly neutralized by the pancreatico-biliary secretions, and any soluble Al would then precipitate as the hydroxide or co-precipitate as the hydroxide–phosphate and become unavailable for absorption. The small amount that is absorbed is either through the gastric mucosa or immediately before precipitation in the proximal small bowel. This theory explains the poor absorption of ingested Al, the efficacy of Al compounds as oral phosphate binders and why certain ligands, such as citrate, that can maintain Al in a soluble form at about neutral pH, may promote absorption of the metal (Weberg & Berstad, 1986).

Nevertheless, only one study has been performed, in the perfused rat, to demonstrate this (Partridge *et al.* 1989), and unfortunately abnormally high levels of the metal were used, probably not even representative of the amount of Al solubilized from pharmacologically ingested doses. Many other metals, such as Cu, Fe and Zn, precipitate at neutral pH and yet are better absorbed than Al. This is because they interact with endogenous ligands in gut secretions that maintain these metals in solution during their transit through the bowel (Gollan *et al*, 1971; Rudzki *et al.* 1973). Citrate (Piper *et al.* 1967), lactate (Piper *et al.* 1967; Powell *et al.* 1990), pyruvate (Piper *et al.* 1967), albumin (Oppenheim, 1970; Clemente *et al.* 1971) and lactoferrin (Dipaola & Mandel, 1980; Nicolai *et al.* 1984) are all present in intestinal secretions and could similarly prevent precipitation of dietary Al during transit. In addition, the binding of trivalent metals, in particular Fe(III), to mucus glycoproteins (mucins) has been investigated since these are

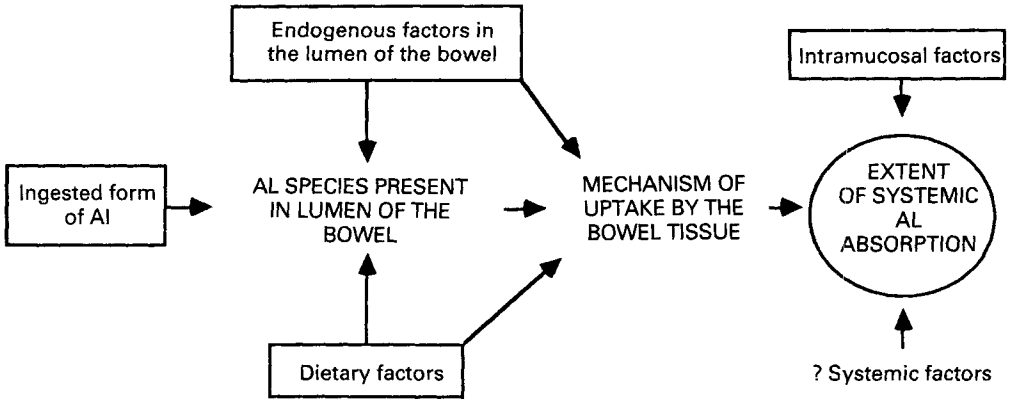

Fig. 1. Four main factors affect the gastrointestinal absorption of Al (□). The chemical speciation of Al in the lumen of the bowel is affected by three of these factors, and is of major importance in determining the mechanism, and so extent, of absorption of Al.

generally bound in preference to divalent metals (Rudzki *et al.* 1973; Crowther & Marriott, 1984; Conrad *et al.* 1991). Although the dissociation constant for Fe (III) binding to mucin is comparatively weak, the total capacity of mucin is high and overall uptake, therefore, efficient (Conrad *et al.* 1991). Fe(III) binds either directly to isolated mucin (Conrad *et al.* 1991) or its precipitation is interrupted by stabilization of colloidal sized hydroxy-Fe species bound to the glycoprotein (Rudzki *et al.* 1973). Al also binds to mucus glycoproteins, at least at acid pH (Crowther & Marriott, 1984), probably via sialic acid end-groups, but this interaction has not been fully studied, so direct interaction with monomeric Al, or stabilization of a polymeric, perhaps colloidal, species are both possible. Hence, the solution chemistry of dietary Al in the lumen of the gastrointestinal tract will be dictated by competition from endogenous factors, such as mucins, albumin and citrate, and, exogenous (dietary) factors.

Many experimental studies have shown a large uptake of Al by the gut but then little absorption (Feinroth *et al.* 1982; Farrar *et al.* 1988; Van der Voet *et al.* 1989). The relative percentages of this Al that are intramucosal and extramucosal have not been elucidated but our own work suggests that at least the latter (i.e. adhesion onto gut mucosa) is one major limiting factor to Al absorption (Powell & Thompson, 1990). This barrier may be largely derived from the overlying insoluble mucus, which avidly binds metals (Quarterman, 1987). Transport of metals through mucus is not understood but fasting increases the absorption of Zn and Fe from the diet (Quarterman, 1987), probably due to an increase of sialic acid residues within the mucus overlying the mucosal surface (Quarterman, 1987). Fasting may similarly, therefore, increase the systemic absorption of Al, as has been suggested from findings with Ga (Farrar *et al.* 1988), used as a proxy for Al.

Thus, under typical dietary situations, the Al species formed in the lumen, and at the mucosal surface of the gastrointestinal tract determine the efficiency of absorption of the metal (Fig. 1). These have not been well studied, but clearly the limited absorption of Al from the diet is due to more complex reasons than rapid precipitation in the lumen.

SITE OF ABSORPTION

It has often been suggested that Al is mainly absorbed from the stomach (Kaehny *et al.* 1977; Fleming *et al.* 1989), based on the hypotheses that Al should only be soluble in the acid stomach and precipitate at neutral pH of the bowel; *in vivo*, however, such precipitation is unlikely. The stomach has a small absorptive area and, at least in the rat, the absorption of Al with citrate occurs from the proximal small bowel (Froment *et al.* 1989*a*). In man, oral-dosing experiments with antacids and citrate (Weberg & Berstad, 1986) show a peak Al concentration in blood at 4 h, suggesting small bowel absorption, since experiments with bismuth citrate-containing compounds achieve peak bismuth concentrations by 30 min (Nwokolo *et al.* 1989), mainly due to absorption from the most proximal small bowel (Nwokolo *et al.* 1989) or some as particles in the stomach (Nwokolo *et al.* 1992). It seems likely, therefore, that Al absorption occurs from the small bowel and not normally from the stomach, although a few metal-containing particles of nanometer diameter are able to penetrate the gastric mucosa (Nwokolo *et al.* 1992). Finally, we have shown that the intestinal lymphoid aggregates (ILA) of the distal bowel in man contain large quantities of sub-micron-sized aluminosilicates (Powell *et al.* 1991) that are almost certainly dietary derived. The role of ILA, which have luminal scavenging activity, requires assessment in disease and perhaps also in the absorption of Al.

MECHANISMS OF ABSORPTION

A number of mechanisms for the absorption of Al have been suggested, but often with poor interpretation of the data. For example, Provan & Yokel (1988) suggested from the effects of various channel-blocking compounds that Al uptake occurs by an energy-independent, Na-dependent, paracellular pathway-mediated process. However, the results more probably showed the effect of various chemicals on a precipitate of Al and its adherence to mucus and mucosa.

Ca inhibits Al absorption and some have postulated, therefore, that Al may share the Ca absorption process (Lote & Saunders, 1991). This is unlikely, since the small size of the Al ion will not favour substitution for the larger Ca ion (MacDonald & Martin, 1988), and the effect of Ca may rather be better maintenance of the paracellular pathway (Froment *et al.* 1989*a*). The size of the Al ion is more like that of Fe(III) and Mg ions (MacDonald & Martin, 1988); but in the rat, Fe(II), and not Fe(III) increases the intestinal uptake and reduces the absorption of Al (Van der Voet & de Wolff, 1987). These latter findings, however, are difficult to interpret since the bowel was perfused at unphysiologically low pH (pH 3) and high rate of flow (10 ml/min); moreover, the speciation of Fe(III) is uncertain even at this low pH. Absorption of Fe(III) probably does not occur actively but instead it is reduced to Fe(II) at the mucosa and is then actively absorbed (Raja *et al.* 1991). However, the size and charge of the Al ion are significantly different from those of Fe(II) and so Al is unlikely to follow this uptake mechanism. The dependence on body Fe status of the systemic transfer of Al is discussed later. Although interactions with intestinal Mg transport have not been studied, the minute absorption of Al and its increase by the concomitant ingestion of citrate (Weberg & Berstad, 1986) do not support its use of an active transport system.

Passive absorption may occur either between enterocytes (paracellular) or through enterocytes (transcellular). Al in the presence of citrate appears to be largely absorbed

by the paracellular pathway through imperfect tight junctions (Froment *et al.* 1989*a*), probably because citrate chelates intramucosal Ca. Not all Al absorption necessarily occurs in this manner, since the Al species present in the lumen of the gastrointestinal tract will dictate how it is taken up by the mucosa. Other potential routes of uptake include persorption (O'Hagan, 1990; paracellular), endocytosis by mucosal cells (O'Hagan, 1990; transcellular) or conventional transcellular transport of hydrophobic or very small hydrophilic species. It is unclear which of these mechanisms predominates for Al in a normal diet.

ABSORPTION OF ALUMINIUM FROM THE GASTROINTESTINAL TRACT IN THE NORMAL POPULATION

A number of patient groups with hyperpermeability of the bowel may be particularly at risk of hyperabsorption of Al. These include patients with renal failure (Lindholm *et al.* 1985), who have more permeable guts (Magnusson *et al.* 1991), infants (Weaver *et al.* 1984; Bishop *et al.* 1989) and those with enteropathy (Lindholm *et al.* 1985). However, the first sound evidence of gastrointestinal absorption of Al from normal volunteers was that of Kaehny *et al.* (1977) by analysis of plasma and urine levels after dosing with different Al compounds. This work used a relatively contaminant-free collection procedure and a sensitive analytical technique (furnace atomic absorption spectrometry), since baseline levels of plasma were quite low (6–7 μg/l). Nevertheless, it was not possible to estimate precisely the amount absorbed because only one elimination route (urine) was studied. A full balance study was then attempted in six men using Al-containing antacids (Gorsky *et al.* 1979). Typically this work is difficult because such a tiny percentage of the Al is absorbed, because of problems with exogenous contaminating Al, either in the diet or during sample collection, and because of the need for highly accurate analyses. The results suggested an apparent positive balance of 23–330 mg Al/d during the ingestion phase (Gorsky *et al.* 1979), in agreement with previous work with Al balances in uraemic patients given large oral loads of Al (Clarkson *et al.* 1972). Clearly these results were gross overestimates of normal retention, either attributable to the problems discussed previously, or to too short a faecal collection time after dosing. A subsequent balance study (Greger & Baier, 1983) indicated that any body burden of Al could not be shown within the error of the study, which is probably a fair summary. Interestingly, for subjects ingesting low (i.e. normal) levels of Al (5 mg/d), 0·78% of this was excreted in the urine, suggesting that at least this small amount is absorbed from the normal diet (Greger & Baier, 1983). However, the average baseline urinary levels of Al (35 μg/d) were slightly high compared with those in subsequent studies, which showed average baseline urinary levels per 24 h of 2·7 and 4·6 μg (Haram *et al.* 1987); 7·56 μg (Weberg & Berstad, 1986); and 9, 12, 29 and 8 μg (Walker *et al.* 1990). These differences may be due to differences in analytical techniques, varying dietary intake, or changes in fluid output, since total urinary Al excretion correlates with urine volume (Greger & Baier, 1983). Thus, a good fluid output may be necessary to achieve an Al output that approximates to the amount absorbed.

At least 1% of Al was absorbed from a dose of 1·1 μg Al coingested with a sodium citrate solution (Day *et al.* 1991), measured with the ^{26}Al isotope in blood by high-energy accelerator mass spectrometry. The lower limit of 1% absorption is based on the peak blood analysis at 6 h, although the peak in blood was probably considerably earlier.

Furthermore, because urinary analysis of ^{26}Al is more difficult it was not reported, but would have given a better estimate of the lower limit of absorption, which in this study was probably higher than 1%. Nevertheless, an extremely low dose of Al was used in a sodium citrate solution, and was not designed to mimic the dietary situation. More importantly, this demonstrated the first use of ^{26}Al, which should avoid the enormous analytical problems associated with standard ^{27}Al and its background concentrations in the body and diet.

A number of single-dosing studies using standard Al have been carried out in man, mainly with antacids (Weberg & Berstad, 1986). However, it is then not known how much Al is in solution in the intestinal lumen and, therefore, even how much is potentially available for absorption. The dissolution of antacids is complex even *in vitro* (Hem & White, 1989) and *in vivo* many physiological factors such as gastric emptying, pH and transit times will greatly affect the degree of solubility of antacids in the stomach. Nevertheless, the fractional absorption of Al, based again on urinary excretion, was 0·007% from one antacid tablet (244 mg $Al(OH)_3$ + 45 mg $MgCO_3$), 0·004% from four tablets, and 0·001% from eight tablets (Weberg & Berstad, 1986). These and other findings (Greger & Baier, 1983; Day *et al.* 1991) suggest, not surprisingly, that the fractional gastrointestinal absorption of Al decreases with increasing dose.

Recent work with non-haem-Fe shows that promoters and inhibitors of absorption (Cook *et al.* 1991) have markedly less effect in a whole diet than when used in isolated absorption studies and, thus, the availability of Al from the average diet is probably between 0·1 and 1% but nearer 0·1%; the lower limit is based on an average urinary excretion of 10 μg/d (Walker *et al.* 1990) and an intake of 8 mg/d (Sherlock, 1989), and the upper limit is based on the results discussed previously (Greger & Baier, 1983; Day *et al.* 1991).

GASTROINTESTINAL ACIDITY AND THE FORM OF INGESTED ALUMINIUM

It has been suggested that an acidic environment promotes the absorption of Al, based mainly on results from *in situ* perfusion of the rat gut (Van der Voet & de Wolff, 1986). However, this experiment probably rather indicates that at the lower pH (pH 4) more Al is in solution, and so absorbed, than at the higher pH (pH 7). This is an oversimplification of the situation *in vivo*, and, moreover, the effect of acid pH on the permeability of the bowel mucosa was not investigated.

The instillation in man of antacids suspended in 70 ml HCl (pH 2·4) did not affect the absorption of Al (Weberg & Berstad, 1986), but in contrast when the gastric pH was raised to 5·9 using intravenous ranitidine (Rodger *et al.* 1991), the absorption of Al from antacids, based on urinary excretion, was greatly reduced. This latter study needs careful interpretation since acidity is required for the dissolution of antacids and again these results probably show that more Al is solubilized from antacids at the lower pH, and not that acid itself increases the absorption of Al. So there is little evidence to suggest that an elevated proton concentration in the stomach/bowel increases Al absorption, but rather that, like Fe (Champagne, 1988), a more acidic gastric environment may help to solubilize more of the ingested Al. Clearly the gastric solubility of Al depends largely on the form in which it is ingested. Aluminosilicates yield little soluble Al even at acidic pH and Al from these is not absorbed (Mauras *et al.* 1983); dissolution and absorption from $Al(OH)_3$ is variable but low (Kaehny *et al.* 1977; Weberg & Berstad, 1986), while

absorption of Al from soluble salts (e.g. chloride, lactate) is slightly higher (Froment *et al.* 1989*b*). The release of endogenous and added forms of Al from various fluids and foods in the gastric environment has not been studied.

FOOD AND DRINKING WATER

In spite of the problems associated with epidemiological studies it is interesting that at least seven studies have so far related elevated Al concentrations in drinking water to an increased rate of Alzheimer's disease (Crapper-McLachan *et al.* 1991). Can Al from drinking water really be more readily absorbed? The same authors (Crapper-McLachan *et al.* 1991) postulate that differences between the organic or inorganic forms of Al should be considered. This seems unlikely. First, Al should be released in the acidic stomach from its waterborne complexes, although due to the slow rates of ligand exchange of the metal and the rapid gastric emptying of fluids, this cannot be assured; second, because the high concentration of endogenous ligands in the bowel will then compete with the generally low concentrations of waterborne organic ligands; and third, because the ligands in water that are generally most avid for Al will reduce its absorption (e.g. fluoride, phosphate, silicic acid). In contrast, some ligands in food may promote the systemic absorption of Al (e.g. citrate, maltol). An alternative theory (Martyn *et al.* 1989) is that Al from drinking water is more absorbable because of its easy solubility, compared with that released and solubilized from food in the gastric environment. This is likely to be true, since food buffers acid in the stomach and is probably a poor source of soluble Al. The question of quantity, however, is even more important. Based on the unlikely scenario of the European Community Directive maximum allowed concentration of Al in water of 200 μg/l, a daily ingestion of 2 litres of such water, and an absorption of 1%, then only 4 μg will be absorbed per d. This is still less than half the Al normally excreted in the urine over the same period. Diet, and when applicable drugs, are, therefore, the likely major source of absorbed Al.

A third and more plausible hypothesis (Birchall & Chappell, 1989) is that these seven epidemiological studies are instead markers of silicic acid intake, since fluids, rather than food, are the major ingested source of Si, and the concentration of silicic acid inversely correlates with the concentrations of Al in drinking water. Silicic acid may well be protective against the effects of Al, so further epidemiological studies should consider this.

PROMOTERS AND INHIBITORS OF ALUMINIUM ABSORPTION

Citric acid

Certain dietary cofactors undoubtedly affect the absorption of Al, although their role in the diet may be considerably less than when studied in isolation. In particular, based on urinary Al excretion, citric acid promoted the systemic absorption of Al from antacids by about fiftyfold in one study (Weberg & Berstad, 1986) and eightfold in another (Walker *et al.* 1990). Significant increases in plasma Al were also noted (Slanina *et al.* 1986; Weberg & Berstad, 1986) after co-dosing citrate and Al, compared with Al alone. The extent of this increase in Al absorption by citrate will depend on the form of Al and the concentrations of Al and citrate. Oral citrate alone only slightly increases serum Al levels

(Slanina *et al.* 1986) or has no effect on the serum levels (Weberg & Berstad, 1986). Clearly the co-ingestion of both citrate and Al are required to increase Al absorption greatly, and there are three possible mechanisms for this effect: (1) Al may be maintained in solution at the neutral pH of the bowel and, thus more will be available for absorption. This is potentially true for large doses of Al, but with dietary levels although some binding of Al to citrate in the lumen is a probable consequence of their co-ingestion, it is unlikely to be for the reason of solubility that citrate promotes the absorption of dietary Al, since many other ligands in endogenous secretions perform this task; but rather because aluminium citrate species are small and could then be well absorbed; (2) citrate and Al may form an uncharged species better able to pass the lipophilic gastrointestinal mucosa (Slanina *et al.* 1986). This seems unlikely, because this species forms only at below pH 4, and predominantly at pH 2·5 (Slanina *et al.* 1986), in other words in the stomach which is an unfavourable site for absorption; (3) citrate may chelate endogenous mucosal Ca and so make the paracellular pathway of the bowel more accessible by opening the tight junctions between the mucosal cells (Froment *et al.* 1989*a*). This is the more likely explanation of the 'citrate effect', perhaps facilitated by the small size of any aluminium citrate species formed.

Other dietary ligands

Just as the enhancing action of dietary citrate on absorption may be partly by binding Al in the intestinal lumen, so other dietary ligands could similarly affect the gastrointestinal uptake of the metal. In principle, ligands must be able to compete with hydroxide, which, at about neutral pH combines with Al to precipitate it out as $Al(OH)_3$. In practice, this probably does not happen in the lumen containing dietary levels of Al, because interactions with endogenous ligands maintain Al truly soluble, metastable, or as a stable colloid form. Nevertheless, polymerization of hydroxy-Al species is a strong driving force, so for dietary ligands to be effective they must at least be able to compete with this process and probably with others, such as the interactions of mucus and Al, protein and Al and the low-molecular-weight ligands and Al. The relative strengths of some typical ligands for Al can be calculated thermodynamically (Ohman & Sjoberg, 1988). Al–ligand interactions depend largely on their relative concentrations and pH, but because of kinetic factors and the possibility of the formation of metastable species, thermodynamic calculations are only a guide and cannot give definitive predictions. For example, if the concentration of lactate (relatively strong; Ohman & Sjoberg, 1988) is favourable, it can compete at least transiently at neutral pH with hydroxide (very strong; Ohman & Sjoberg, 1988) by the formation of a metastable species (Corain *et al.* 1992). The following potential ligands have been studied for their effect on the systemic absorption of Al.

Silicon

Within our lithosphere Al is found mainly as inert aluminosilicates. The interaction between Si, Al and O is so strong that even today there are no economical methods for the extraction of Al from these minerals. However, soluble Si is available, as silicic acid, theoretically up to 120 mg/l in water (Carlisle, 1982), and clearly solution chemistry between these elements (Si, Al and O) occurs (Chappell & Birchall, 1988), if only as a

precursor to the formation of aluminosilicates. The Si present in food is less available to interact with Al than that within fluids, for example drinking water, where it is mainly monomeric silicic acid (Birchall & Chappell, 1989). The concentrations of silicic acid in drinking water varies from 0·5–14 mg/l, depending on the origin of the water (Birchall & Chappell, 1989), so 1 litre of drinking water will yield 18–500 μmol silicon. Assuming that as much as 10% of dietary Al (0·8 mg/d) is available in the lumen of the gastrointestinal tract, then the molar ratio of Si:Al is up to 30:1. This general excess of Si over Al, particularly at the higher ratios, may be important, since these elements are then able to interact in solution (Chappell & Birchall, 1988). Furthermore, the solution chemistry is enhanced in the presence of bicarbonate (Chappell & Birchall, 1988) which is secreted by the bowel and in pancreatic juice. Metastable aluminosilicates may be formed in solution, and these hydroxyaluminosilicates are considerably less available; for example they limit the toxicity of Al to the gills of fish (Birchall *et al.* 1989), probably by preventing the interaction of Al with mucus or epithelium (Birchall *et al.* 1989).

In the gut there is a large number of other chemical species that may interact with Al and their competition with Si for Al is strongly pH dependent (Birchall, 1990). Intestinal pH varies in both the lumen and the microclimate of the bowel between pH 6 and 7·5, which is exactly where silicic acid competes well with phosphates and even with citrate (Birchall, 1990). Since oral Si appears to be protective against accumulation of Al in the ageing brain of the rat (Carlisle & Curran, 1987), it is, therefore, plausible that dietary Si and Al interact in the gastrointestinal tract, and so the importance of silicic acid in our diet against other potentially limiting factors, such as phosphate, phytate and polyphenols of tea requires investigation.

Phosphate and phytate

The stability of $AlPO_4$ and the use of oral Al compounds (hydroxide and hydroxycarbonate) as phosphate binders (Kaye & Gagnon, 1985), indicate that Al and P form strong complexes. In the gastrointestinal tract, phosphate probably adsorbs onto the positively charged surface of $Al(OH)_3$ or hydroxycarbonates (Liu *et al.* 1984). In contrast, the adsorption of dietary Al onto phosphate is less certain, since so many other negatively charged species are available and phosphate with such a large surface area is unlikely to be available.

Solution chemistry between Al and various phosphates is demonstrable (Goldshmid & Rubin, 1978), but around neutral pH a precipitate is dominant (Erdman & Poneros-Schneier, 1989). Thus, similarly to the hydroxide of Al, it is more likely that other endogenous and dietary ligands prevent or interfere with the growth of aluminium hydroxyphosphate species. Furthermore, other cations such as Ca, could compete for phosphate. The expected effect of dietary inorganic phosphate, if at all, is to limit the systemic absorption of Al, but further work with *in vivo* absorption studies is required.

Phytic acid is the hexaphosphate of *myo*-inositol and is present in food, particularly cereals (Erdman & Poneros-Schneier, 1989). It is a strong chelating agent for a number of metal ions (Kratzer & Vohra, 1986; Erdman & Poneros-Schneier, 1989) and forms a stable and readily precipitable complex with Fe(III) (Kratzer & Vohra, 1986). Its interactions with metal ions reduces their bioavailability (Erdman & Poneros-Schneier, 1989) and so its effect on the absorption of Al also requires study.

Maltol (3-hydroxy-2-methyl-4 pyrone) and fluoride

Maltol and fluoride are both dietary agents that form strong complexes with Al (Ohman & Sjoberg, 1988). Maltol is used as a flavouring agent in some foodstuffs, and is also a natural product of caramelization. Maltol significantly increases the absorption of oral Ga (used as a proxy for Al) in fasted rats (Farrar *et al.* 1988), while fluoride decreases it (Farrar *et al.* 1988). Using everted gut sac experiments, these opposing actions of fluoride and maltol were shown not to be different effects on the uptake by mucosa, but rather on its subsequent transfer (i.e. absorption). Since both maltol and fluoride favour the formation of small Al complexes, the reason for these differences are not clear but may be related to overall species charge or, again, intramucosal Ca chelation. The average daily intake of fluoride is less than 2 mg/d (Walters *et al.* 1983) and so important interactions with Al in the lumen will be limited.

Other ligands

Al in tea infusion is partly bound to polyphenols, possibly thearubigens (Baxter *et al.* 1989). Although some work has suggested that the absorption of Al after tea drinking is increased (Koch *et al.* 1988), this measured total Al in 24 h urine and did not take into account the diuretic effect of tea, nor has it been supported in studies with rats (Fairweather-Tait *et al.* 1991). Tea inhibits the absorption of non-haem-Fe from the diet (Disler *et al.* 1975; Fairweather-Tait *et al.* 1991) and it is possible that a similar inhibitory effect on absorption of Al from other dietary sources is seen when food is taken with tea.

Based on empirical *in vitro* observations, it has been suggested that a number of low-molecular-weight carboxylates in the diet may bind Al, namely ascorbic, citric, gluconic, lactic, malic, oxalic and tartaric acids (Partridge *et al.* 1989). These may bind strongly, such as citrate, or induce metastable species, such as lactate and probably ascorbate. Compared with a control group of animals receiving only $Al(OH)_3$, all these ligands increased tissue concentrations, but surprisingly not the urinary output, of Al when they were separately added to the drinking water of rats similarly receiving $Al(OH)_3$ (Domingo *et al.* 1991*a*). Experiments in rabbits (Fulton & Jeffery, 1990) and man (Domingo *et al.* 1991*b*) show that ascorbate increases the urinary excretion of Al. If interaction of these ligands with Al in the lumen promotes its absorption, then the quantities ingested are important in determining whether they interfere with Al as it passes through the gastrointestinal lumen. Lactate and ascorbate would need, therefore, to be in greater concentration than citrate to compete for Al. The effects of these ligands on binding Ca should also not be ignored. The overall charge of the species formed is not known, but the small size of the Al complexes could be an important factor in helping to promote Al absorption. Finally, even certain large molecules such as lactoferrin need to be considered, since this protein promotes the absorption of a number of metals, for example Pb (Quarterman & Morrison, 1985).

Effect of iron status

Based on the similar chemistry of Al and Fe(III), it has been postulated that Al may share with Fe some mechanisms of intestinal absorption, and that this may be affected by

the individual's efficiency of the Fe-absorptive mechanism (Cannata *et al.* 1984). Although Al is not related to mucosal uptake of Fe(III) (see p. 243), its subsequent systemic transfer may be partly modulated by the Fe status of an individual. Fe absorption is itself probably controlled by circulating humoral mediators related to body Fe status (Apte & Bown, 1969; Conrad, 1969; MacDermott & Greenberger, 1969) and by intestinal mucosal Fe stores (Conrad & Crosby, 1963; Adams *et al.* 1991). Similarly, Fe status (determined by ferritin levels) inversely predicts absorption of Al (Cannata *et al.* 1984), and this appears to be partly related to Fe status of the intestinal mucosal cells, which in culture take up significantly more Al when Fe-deplete (Menendez *et al.* 1991). This Fe depletion of mucosal gut cells is probably a risk factor in enhancing the systemic absorption of at least transcellularly entering Al.

CONCLUSION

Dietary Al in the lumen of the stomach is composed of a portion that is broken down and solubilized by acid and that which passes down the gastrointestinal tract in its ingested insoluble form. The stomach is not an important site for absorption of Al, which mainly occurs in the small intestine. Solubilized Al in the small intestine will bind to endogenous intestinal species such as lactoferrin, lactate and mucins. The interaction with mucins may be stoichiometric or only by stabilization of polymeric $Al(OH)_3$; simple precipitation of $Al(OH)_3$ does not occur. Dietary ligands may then compete with these endogenous Al-ligand interactions in the bowel to form other Al species which, depending on the ligand, may promote or further inhibit systemic absorption. Some dietary factors may also have non-ligand effects on absorption of Al, e.g. the chelation of intramucosal Ca by citrate. Al is passively absorbed from the bowel and the species of Al in the lumen and some non-ligand factors will dictate whether the route of absorption is paracellular or transcellular, and thus the efficiency of absorption. The average absorption of Al from the diet is probably around 0·1% (10μg/d).

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