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Coordination Chemistry Reviews
149 (1996) 231–240

COORDINATION CHEMISTRY REVIEWS

On the mechanisms underlying the essentiality of silicon — interactions with aluminium and copper

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Received 25 January 1995

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Abstract

Silicon was confirmed as an essential element in experiments (1972) in which rats and chicks fed on a silicon-depleted diet showed reduced weight gains and pathological changes in the formation and structures of collagenous connective tissue and bone. The biochemical mechanisms underlying the effects of silicon deficiency have until recently been obscure, with no evidence for any organic binding of silicon.

Recent studies have shown that silicic acid, $Si(OH)_4$, the form in which silicon exists in physiology, interacts with aqueous aluminium species to form hydroxyaluminosilicates that can have low bio-availability and toxicity. It is now established that the gastro-intestinal absorption of aluminium is greatly reduced in the presence of silicic acid. More recent studies indicate that the intake of dietary silicic acid also influences the excretion of aluminium via the kidneys so that silicon appears to be profoundly involved in aluminium homeostasis. There are strong indications that silicic acid promotes copper utilization. The observed effects

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SSDI 0010-8545(95)01155-2

of silicon deficiency on collagen and osteogenesis may thus be due to low copper utilization. Whether reduced copper utilization is caused by aluminium so that it is enhanced by silicic acid via the latter's interaction with Al is uncertain. Future research should include the interactions between Si, Al and Cu.

Keywords: Silicon; Silicic acid; Aluminium; Copper; Collagen; Excretion

1. Introduction

1.1. Early work on silicon essentiality

Silicon, the second most abundant element in the earth's crust after oxygen, is listed as an essential element. This followed the researches of Schwarz and Milne [1] and Carlisle [2], who maintained rats and chicks, respectively, on a silicon-depleted diet and observed low weight gains and defective bone development in the animals, with collagen formation in connective tissue and the pre-osseous matrix altered in the Si-deficient animals. The earliest theory as to the mechanism of such effects arose from analytical studies which suggested that isolated biopolymers of connective tissue (collagen, glycosaminoglycans, etc.) contained tightly bound silicon and that siloxane bridges formed cross-links between biopolymer chains, e.g.

$$R_1\text{–O–Si–O–}R_2$$

and thus influenced the tertiary structure of connective tissue.

However, this idea proved to be wrong, as improved analytical techniques showed that the silicon content of connective tissue and isolated components was very low [3]. Other researches, prior to the key experiments of Schwarz and Carlisle, indicated an effect of silicon on connective tissue formation, and in particular on the structure of the artery wall and the integrity of the elastin component [4–6]. It is, of course, usual that the inorganic elements (Zn, Fe, Cu, etc.) are bound within the protein components of enzymes, etc., but no organic binding of silicon has been demonstrated in physiology, either as Si–C or stable Si–O–C bonds. How then does silicon in the form of silicic acid, $Si(OH)_4$, influence collagen formation, the structure of connective tissue, osteogenesis, etc.?

2. The interaction of silicic acid with other metal ions

2.1. Interaction with aluminium

Silicon exists in the earth's crust as silica and silicates, especially in the alumino-silicates of rock and soil minerals. Such solid phases release silicon into the aqueous environment as silicic acid, $Si(OH)_4$. This is a sparingly soluble species below pH 9, 2 mM, above which silanol condensation

$$\equiv\text{Si–OH} + \text{OH–Si}\equiv \rightarrow \equiv\text{Si–O–Si}\equiv + H_2O$$

produces oligomeric silicic acids and eventually particles and gels of hydrated silica,

$SiO_2 \cdot xH_2O$, such as are found in plant phytoliths. The form of silicon most available to biology is thus "dissolved silica" or silicic acid. The "silicon cycle" is described in Ref. [6], which also reviews early thinking.

With no strong organic binding of silicon being found in biology, it is necessary to investigate the inorganic chemistry of silicic acid, the species present in physiologically relevant ranges of concentration and pH. Solid, hydrated silica, $SiO_2 \cdot xH_2O$, does exist in biology in plants and in siliceous diatoms. In plants, silicic acid in soil water is carried in the transpiration stream and polymerised in extremities as phytolithic silica. In diatoms, silicic acid is polymerised within space delineated by membranes to form the frustule. However, in animal physiology, silicon is absorbed in the gastro-intestinal tract as monomeric silicic acid, circulated in that form and excreted via the kidney in that form. At the concentration and pH range found in physiology, silicic acid has little chemistry: Si–O–C bonds are hydrolytically unstable, although associations via hydrogen bonding are possible.

However, silicic acid interacts with basic metal species, and in particular with basic aluminium species, i.e. $[Al(H_2O)_5(OH)]^{2+}$ to $[Al(OH)_4]^-$, to form hydroxyaluminosilicate species and, ultimately, to form amorphous solids such as proto-imogolite, allophanes and the crystalline, tubular solid imogolite, $(HO)_3Al_2O_3 \cdot SiOH$ [7]. The formation of solids in aqueous solutions containing $Si(OH)_4$ and basic aluminium species at concentrations relevant to water chemistry and to physiology is slow, but sub-collodial species form early [8–10], and their formation does influence the bio-availability of aluminium. This was first demonstrated in experiments in which fish were exposed to low concentrations (about 10 μM) of aluminium in acidic water (pH 5) with and without silicic acid [11]. Without silicic acid, fish mortality was 100% as a result of extensive damage to gill structure and function: when 100 μM silicic acid was present, no deaths occurred, gill structure remained intact, and systemic aluminium absorption into bone, brain and other organs was inhibited. Concentrations of silicic acid less than 100 μM showed a reduced protective effect, a finding explained by subsequent work which showed 100 μM to be required for the formation of stable hydroxyaluminosilicate species [12].

This work led to a general hypothesis: that the essentiality of silicon is related to the ability of silicic acid to restrict the bio-availability of aluminium [13]. The ability of silicic acid to restrict the absorption of aluminium on gill membranes and its transport across gill membranes led specifically to the hypothesis that silicic acid would restrict the absorption of dietary aluminium in the gastro-intestinal tract [11].

This hypothesis has been elegantly confirmed by Edwardson et al. [14]. ^{26}Al contained in orange juice was given to volunteers with and without the addition of 100 μM silicic acid (the minimum required to form stable hydroxyaluminosilicates), and plasma levels determined after 1 and 6 h. The results showed that the presence of silicic acid reduced absorption to 15% of that observed in the drink without the silicic acid addition. This was in spite of the presence of citrate, which is known to enhance the absorption of aluminium. Thus it is now well established that the bio-availability of aluminium is very considerably reduced when hydroxyaluminosilicates form, with their formation requiring a minimum silicic acid concentration of 100 μM. The most stable of these species (proto-imogolite) have a Si:Al ratio of 0.5 and, as

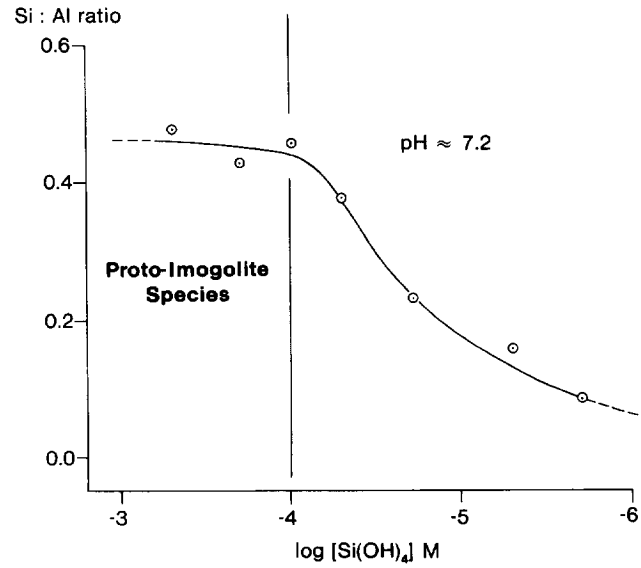

Fig. 1. Si:Al ratio of hydroxyaluminosilicate phases formed at various concentrations of silicic acid: pH 7.2, 20 °C, 10 mM Al. The ratio 0.5 corresponds to proto-imogolite phase.

shown in Fig. 1, require an Si concentration of at least 100 μM Si. These species take time to form, so that contact time (Al/silicic acid) has an important bearing on the bio-availability of aluminium.

2.2. *Epidemiological considerations*

Epidemiological studies [15,16] have indicated an association between the aluminium content of drinking water and the incidence of Alzheimer's disease, although water provides only a fraction of the total dietary aluminium from all sources. It has been proposed, in resolution of this paradox, that this finding reflects the effect of the silicic acid concentration in water (which varies regionally from less than 10 to more than 100 μM) on the absorption of the aluminium in the *total* diet [17]. Aluminium tends to be present in low concentration in silicon-rich waters (and vice versa), and ignoring this effect would give a weak link between disease incidence and aluminium. Initial epidemiological studies in Canada have provided some indication of a "protective" effect of silicon [18].

3. The kinetics of silicic acid absorption and excretion

The finding that silicic acid restricts the gastro-intestinal absorption of aluminium when co-present at 100 μM or above suggests that an understanding is required of (a) dietary sources of silicon, (b) the availability of that silicon, and (c) the kinetics

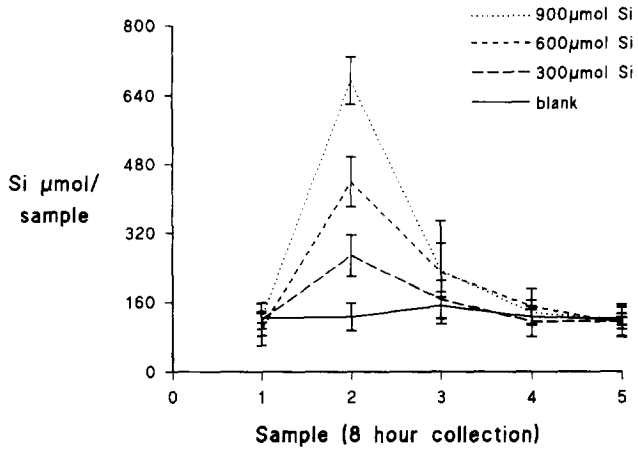

Fig. 2. Mean urine silicon excretion in four healthy volunteers following the consumption of 500 ml water containing 0, 300, 600 and 900 μmol of silicic acid.

of absorption, plasma concentration change and excretion via the kidney. It is clear that "dissolved silica" (i.e. silicic acid) provides the most available form in water and drinks. The daily intake of silicon has been estimated at 30 mg, with 60% of this from cereals and 20% from water [19]. Little is known of the availability for absorption of the various forms of silicon present in dietary components, but recent experimental work has confirmed the ready absorption of the "dissolved silica" in water and in beer, which is rich in silicic acid extracted ("pre-digested") from the cereals used in the brewing process [20].

Fig. 2 shows the pattern of urinary silicon excretion following the consumption of effectively 0, 300, 600 and 900 μM silicic acid. Peak urine excretion was reached in 8 h following ingestion, with a return to background levels within 24 h of ingestion. Similarly, plasma Si levels (usually in the range 5–10 μmol l^{-1}) peak within hours (to 50 μmol l^{-1}) and rapidly decline.

In the course of this study [21], urine aluminium levels were measured, with a surprising result illustrated in Fig. 3. This shows urine aluminium excretion following the administration of 600 μM silicic acid in either beer or water. A peak in urine aluminium is observed, corresponding to peak silicon excretion. The consumption of pure water did not produce this effect. The diuretic properties of alcohol and simple urine volume output are clearly not responsible for enhanced aluminium excretion, which appears to be related to silicon excretion. This is the first indication that silicon (as silicic acid) not only restricts the gastro-intestinal absorption of aluminium but is also involved in the excretion of aluminium via the kidney, and hence has a key role in aluminium homeostasis.

3.1. The mechanism of this effect of Si on Al urine excretion

The mechanism by which silicic acid restricts the gastro-intestinal absorption of aluminium is postulated to be the formation of hydroxyaluminosilicate species, the

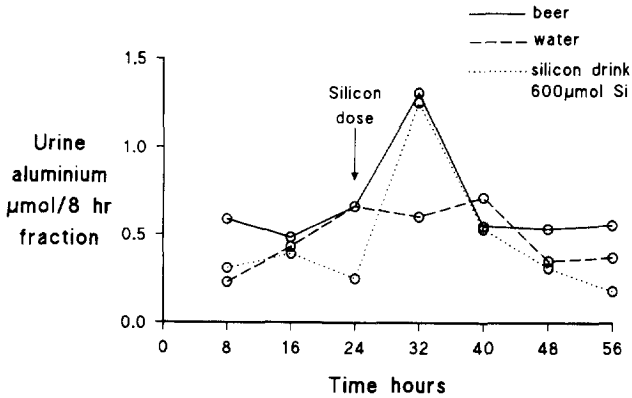

Fig. 3. Urine excretion in healthy volunteers following the consumption of equal volumes of: beer (4.1% alcohol) containing 600 μmol Si per dose (mean urine excretion for six individuals); water (blank) with 4.1% alcohol added and containing negligible Si and Al (mean urinary excretion for two individuals); silicon drink, water with 4.1% alcohol added and containing 600 μmol Si per dose (mean urinary excretion for two individuals).

rapid and stable formation of which requires a minimum of 100 μM Si. This level is seldom attained in plasma, so that hydroxyaluminosilicate formation in plasma (in competition with other ligands such as transferrin, citrate, etc.) is extremely unlikely. Thus silicic acid at the normal concentration in plasma is probably unable to enhance the concentration of that fraction of plasma aluminium that is in low-molecular-weight, excretable form. However, the concentration of silicic acid in urine rarely falls below 100 μmol l^{-1}, and rises to 200–300 μmol l^{-1} following a silicon-rich drink. Thus aluminium excreted into the tubular fluid in the kidney *can* there interact to form hydroxyaluminosilicate species. This could restrict the re-absorption of aluminium and thus transiently enhance its excretion. This would seem to account for the pulse in silicic acid urine excretion, following the consumption of a silicic acid-rich drink, being accompanied by a pulse in urine aluminium excretion.

The analytical problem in following the clearance of aluminium from plasma is formidable, but can be overcome by using ^{26}Al and accelerator mass spectrometry. The results of an experiment in which an oral dose of ^{26}Al was given and plasma levels monitored with time are shown in Fig. 4. With the aluminium clearance rate established, an oral dose of water containing silicic acid (intake 600 μM) was administered. The rise in plasma silicon concentration is clearly seen, and peak Si plasma concentration is accompanied by a transiently increased rate of aluminium clearance from the plasma. A similar effect is produced by the administration of citrate. These experiments strongly suggest that dietary silicic acid influences the homeostasis of aluminium — its absorption, tissue distribution, excretion and hence accumulation.

The clearance of absorbed silicic acid is rapid, suggesting that a regular, high intake (e.g. Si-rich water) will be required to influence aluminium homeostasis continuously.

If it is established that aluminium accumulation influences the pathogenesis or

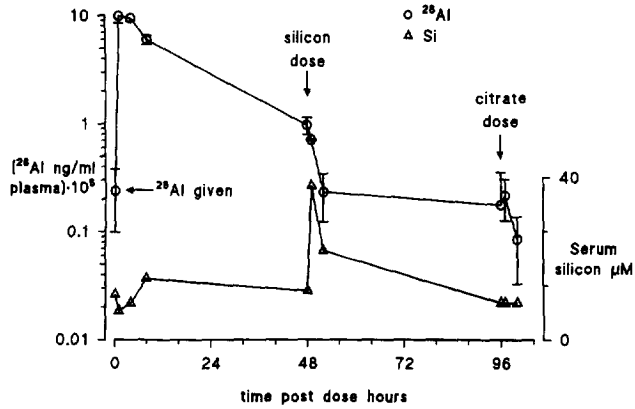

Fig. 4. Clearance of ^{26}Al from human plasma following an oral dose and the effect of subsequent oral doses of silicon (600 μmol in water) and citrate (23 mmol in water).

progress of Alzheimer's disease (or other pathology) then it is evident that the influence of silicon (as silicic acid) on aluminium homeostasis will assume considerable importance.

4. Multi-element interactions, Si→Al→?

Is the interaction of silicic acid with aluminium sufficient to explain the observed effects of silicon deficiency on experimental animals? A consistent finding over many years (pre-dating the work of Schwarz and Milne [1] and Carlisle [2]) has been an association between silicon and connective tissue synthesis and function, including effects on the integrity of the elastin component of the artery wall — for review, see Ref. [6]. Recent work has suggested that such effects may be due to the ability of silicic acid to influence the absorption/utilization of other metals that are vital co-factors in enzymes involved in connective tissue synthesis and structure, in particular copper. For example, there is evidence that, in rats fed water containing aluminium, aluminium accumulation in intestinal cells interferes with the intestinal absorption of copper [22]. Since silicic acid blocks the intestinal absorption of aluminium, an adequate dietary intake of silicic acid may prevent this effect of aluminium.

Further, recent studies have shown that silicic acid influences zinc and copper homeostasis in the rat [23]. Silicic acid was found to increase elastin concentration in the aorta of copper-deficient, zinc-adequate rats, and further studies [24] showed an effect of silicic acid in increasing the utilization of copper even in apparently copper-adequate rats. Thus, 540 mg SiO_2 per kg diet produced a two-fold increase in plasma copper concentrations, a three-fold increase in ceroplasmin activity and an increase in cardiac, renal and hepatic copper concentrations. The aortic dry mass

and elastin content was increased by dietary silicon supplements, and cardiac hypertrophy was reduced.

These effects of silicic acid on copper may at last provide an indication of the mechanism by which silicon deficiency produces changes in connective tissue synthesis and structure, osteogenesis, the integrity of arterial elastin, etc. [25]. Lysyl oxide is the key copper-containing enzyme in the cross-linking of collagen and elastin, and the activity of this enzyme could be reduced by low copper availability. It has been noted that the accurate diagnosis of marginal copper deficiency or defective copper utilization has yet to be perfected, with serum copper concentration being a much-used but inadequate index [26].

An important question is: is the "activation" of copper utilization promoted directly by silicic acid, or indirectly via its effect on aluminium and with aluminium depressing copper utilization? There is some evidence for the latter in recent results. These are summarized as follows:

(1) At least some of the disorders attributed to aluminium in renal dialysis patients could be associated with defective copper utilization, notably the anaemia in which impaired copper utilization would result in defective iron metabolism. Cardiac hypertrophy [27] may be associated with aluminium accumulation in the heart in dialysis patients [28], and is a feature of copper deficiency. At least some aspects of the pathology of dialysis osteomalacia — in which aluminium deposition in bone is observed — may be associated with defective copper utilization. Decreased copper concentration in the tibia of silicon-deprived rats has recently been observed [29].

(2) Decreased serum copper levels have been found in AD patients associated with a higher proportion of serum aluminium bound to transferrin, and thus potentially able to enter the brain [30].

5. Discussion

It appears that silicon (as silicic acid) (a) influences aluminium homeostasis by reducing gastro-intestinal absorption and enhancing excretion via the kidney, and (b) enhances copper utilization. It is difficult chemically to propose a *direct* effect of silicic acid on copper metabolism, and thus it seems a reasonable hypothesis to suggest that copper utilization (absorption, transport, delivery to cells) is affected by aluminium and thus mediated by silicic acid, which determines aluminium homeostasis. This it does by limiting gastro-intestinal Al absorption and enhancing excretion. The indications are that aluminium excretion is enhanced, not because aluminosilicates are formed in *plasma* in which silicic acid concentration is too low, but because they form in the kidney tubular fluid, which, following an oral dose of silicic acid, contains well in excess of the minimum concentration of 100 μM Si required for stable hydroxyaluminosilicate formation. These species have been shown not to be absorbed by the fish gill membrane nor by the membranes of the gastro-intestinal wall, and thus are probably not re-absorbed in the kidney tubule.

Aluminium urine excretion is thus associated with peak Si excretion in urine. Indeed, a study of the urine excretion of Al and Si after renal transplant has suggested

such an association, and concluded that elevated serum Si can assist the rapid clearance of accumulated aluminium following kidney transplant [31]. In the present study, an oral dose of citrate produced an increase in the rate of aluminium clearance from the plasma (Fig. 4). This is in agreement with the finding that, in aluminium-loaded rats, citrate excretion in urine was directly associated with increased aluminium excretion [32]. This effect was attributed to changes in the handling of aluminium by the kidney. It is now clear that this effect was produced by silicic acid in healthy human subjects not overtly loaded with aluminium. Furthermore, citrate is known to enhance the gastro-intestinal absorption of aluminium [33], whereas silicic acid inhibits absorption, and this, together with its inducement of enhanced excretion, suggests an important role for dietary silicic acid in aluminium homeostasis.

It is clear that much further work is required to elucidate (a) the kinetics of aluminium absorption/excretion and its distribution in tissue and plasma, and the effect of silicic acid intake on these parameters, and (b) the effect of aluminium on copper homeostasis, thus establishing whether the observed effects of silicon on copper utilization are mediated via aluminium. In addition, with 100 mM being the minimum silicic acid concentration required to suppress Al gastro-intestinal absorption and kidney tubule re-absorption, the importance of dietary sources of *available* silicic acid (e.g. water) and the frequency of intake require investigation.

Three-element interactions have been described previously [34], i.e. Al, P, Si, in which the ability of aluminium to limit the bioavailability of essential phosphate is reduced when silicic acid is present and hydroxyaluminosilicates are formed. There are now strong indications that interactions in the triad Al, Si, Cu may be of profound physiological significance, with silicic acid possibly blocking effects of aluminium on copper utilization.

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