Silicon Reduces Aluminum Accumulation in Rats: Relevance to the Aluminum Hypothesis of Alzheimer Disease

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Summary: In recent years, a possible relation between the aluminum and silicon levels in drinking water and the risk of Alzheimer disease (AD) has been established. It has been suggested that silicon may have a protective effect in limiting oral aluminum absorption. The present study was undertaken to examine the influence of supplementing silicon in the diet to prevent tissue aluminum retention in rats exposed to oral aluminum. Three groups of adult male rats were given by gavage 450 mg/kg/day of aluminum nitrate nonahydrate 5 days a week for 5 weeks. Concurrently, animals received silicon in the drinking water at 0 (positive control), 59, and 118 mg Si/L. A fourth group (–Al, –Si) was designated as a negative control group. At the end of the period of aluminum and silicon administration, urines were collected for 4 consecutive days, and the urinary aluminum levels were determined. The aluminum concentrations in the brain (various regions), liver, bone, spleen, and kidney were also measured. For all tissues, aluminum levels were significantly lower in the groups exposed to 59 and 118 mg Si/L than in the positive control group; significant reductions in the urinary aluminum levels of the same groups were also found. The current results corroborate that silicon effectively prevents gastrointestinal aluminum absorption, which may be of concern in protecting against the neurotoxic effects of aluminum. Key Words: Aluminum—Silicon—Oral exposure—Rats—Tissue retention—Urinary excretion.

Although the association between aluminum exposure and Alzheimer disease (AD) and related disorders remains unproven (Good and Perl, 1993; Forbes et al., 1995; Storey and Masters, 1995; Savory et al., 1996), a series of reports in the recent literature strongly suggest that, by limiting human exposure to unnecessarily high aluminum concentrations, the incidence of AD might be reduced (Harrington et al., 1994; McLachlan, 1995; McLachlan et al., 1996).

Recent investigations have suggested that aluminum might directly influence the process of aggregation and the deposition of senile plaques by accelerating the proteolytic processing of the β-amloid precursors protein by suppression of the inhibition domain. The β-amloid peptide, the major component of senile plaques in the brains of AD patients, might then accumulate, and because it has an intrinsic tendency to form insoluble aggregates, the plaque formation would be initiated (Clauberg and Joshi, 1993; Kawahara et al., 1994; Vyas and Duffy, 1995). The possibility that aluminum may play some role in neurofibrillary tangle formation by acting on tau has also been suggested (Abdel-Ghany et al., 1993).

In recent years various studies have related elevated concentrations of aluminum in drinking water to an increased incidence of AD or cognitive impairment (Martyn et al., 1989; Forbes et al., 1995; Jaegmin-Gadda et al., 1996; McLachlan et al., 1996). With regard to the potential association between aluminum, water chemistry, and AD, Birchall and Chappell (1989) suggested that the geographical association between aluminum and the disorder may depend on the level of silicic acid.

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in drinking water. A high intake of silicic acid would be expected to limit the aluminum absorption from drinking water and/or other dietary sources in the alkaline environment of the intestine, thereby preventing the formation of aluminosilicate species. That hypothesis was partly corroborated in a recent epidemiological study (Jacqmin-Gadda et al., 1996). However, in that study the protective effect of silicon was only demonstrated against the aluminum from drinking water as opposed to protection against all dietary sources.

Silicon, a biologically important element that is soluble in water as silicic acid [Si(OH)₄]⁻¹, has been detected in various human tissues, and it is also a normal component of serum (Birchall and Chappell, 1988). Although silicic acid was found to diminish the toxic effect of aluminum in fish as the result of forming hydroxyaluminosilicates (Birchall et al., 1989), administration of dietary silicon also reduced aluminum accumulation in the brains of rats orally exposed to aluminum (Carlisle and Curran, 1987).

At present, it is well established that an increased level of both aluminum and silicon are associated with senile plaques in AD, resulting in the final formation of aluminosilicates in the brain (Birchall, 1992; Savory et al., 1996), whereas it has also been shown that dissolved silicon is an important factor in limiting the absorption of dietary aluminum (Edwardson et al., 1993). In fact, although there is evidence that silicon is relevant to the etiology of AD (Birchall, 1992; Forbes and Agwani, 1994), it is not quite clear how aluminum causes toxicity or the manner in which silicon can affect the biotoxicity of aluminum. Silicon and aluminum coexist in serum with ordinarily an excess of silicon concentration over the aluminum level.

To extend the information on the potential interaction between aluminum and silicon on tissue aluminum retention, the present study was undertaken to evaluate the effects of dietary silicon on the gastrointestinal absorption and tissue accumulation of aluminum.

**METHODS**

Male Sprague-Dawley rats (Interfauna Ibérica, Barcelona, Spain) weighing 210–225 g were used. Animals were housed in a room equipped with automatic light cycles (12 h light/dark) and maintained at a temperature of 22 ± 2°C and relative humidity with a range of 40–60%. Food (Panlab rodent chow, Panlab, Barcelona) and tap water were available ad libitum.

Aluminum was administered as aluminum nitrate nonahydrate (E. Merck, Darmstadt, Germany). Silicon was given as sodium silicate solutions (Aldrich, Steinheim, Germany) containing a 27% of SiO₂. After 1 week of acclimation to the animal room conditions, rats were divided into four groups (10 per group). Animals in three groups were given by gavage 450 mg/kg/day of aluminum nitrate in two equally divided doses (at 10:00 A.M. and 5:00 P.M.) 5 times a week for 5 weeks. The aluminum doses were approximately equal to one-eighth the oral LD₅₀ of aluminum nitrate nonahydrate (Llobet et al., 1987). Concurrently, animals in those groups received silicon in the drinking water at 0 (positive control group), 59, and 118 mg Si/L. The fourth group did not receive oral aluminum or a supplement of silicon and served as the negative control group. The choice of the silicon doses was based on previous experimental studies (Carlisle and Curran, 1987). During the experimental period, the average silicon content of the tap water was 3.5 mg/L, and the pH was 6.5–7.

After 5 weeks, aluminum and silicon administration was ended, and animals were placed in individual plastic metabolic cages, which permitted separate collection of urine and feces. Urines were collected for 4 consecutive days. All animals were then killed by overexposure to diethyl ether, and brain, liver, bone (femur), spleen, and kidney were removed. One-half of each brain was immediately dissected into different regions including cortex, hippocampus, striatum, cerebellum, thalamus, olfactory bulb, and rhinal bulb. Samples were stored at −70°C until used for aluminum analysis. Wet tissues were weighed and placed in a tube that had been rinsed five times in ultrapure water with ultrapure nitric acid (Suprapur, E. Merck) and heated under pressure to accomplish digestion. Urine and tissue samples were then brought to a 10-mL volume with ultrapure water. To eliminate aluminum contamination as much as possible from the environment, all specimen manipulations were performed in a laminar flow hood located in a clean limited-access room. Urine and tissue aluminum concentrations were determined by inductively coupled plasma spectrometry (Thermo Jarrell ASH, PolyScan 61E). Blank tests were conducted using nitric acid instead of the urine or tissue samples, treated as described above. The recovery of aluminum exceeded 96% for all the samples processed, whereas the coefficients of variation were between 4.6 and 6.8%.

Test groups were compared with both negative and positive control groups by means of one-way analysis of variance, with significant F values analyzed further using the Mann-Whitney U test. A probability value of p < 0.05 was considered to be significant.

**RESULTS**

Aluminum concentrations in selected tissues of rats concurrently exposed to aluminum nitrate by gavage
and silicon in drinking water for 5 weeks are shown in Table 1. In all groups the highest aluminum levels were found in bone, spleen, and kidney. By contrast, aluminum in the brain was only detected in the positive control group (+Al, −Si). In that group, tissue aluminum concentrations were significantly higher than in the other three groups. Rats supplemented with silicon in drinking water showed a significant reduction in the aluminum tissue levels (with the exception of liver and kidney in the group given 59 mg Si/L) in relation to those in the negative and the positive control groups. The most remarkable reductions were observed for animals receiving the highest silicon concentration.

Aluminum levels in different brain regions of rats given aluminum and silicon are summarized in Table 2. In the control groups the highest aluminum concentrations were found in the olfactory bulb followed by the rhachidical bulb and the cerebellum, whereas the hippocampus (both groups), striatum (+Al, −Si), and cortex (−Al, −Si) were the regions showing the lowest aluminum concentrations. A similar pattern was also found in the group exposed to aluminum and 59 mg Si/L; surprisingly, at 118 mg Si/L the olfactory bulb was one of the cerebral regions showing the lowest aluminum level. Although in all regions aluminum administration significantly enhanced the aluminum levels, they were reduced significantly by silicon supplementation. In addition, at 118 mg Si/L, most aluminum levels were even significantly decreased with regard to those observed in the negative control group (−Al, −Si).

The effect of silicon supplementation on the cumulative (4 days) urinary aluminum excretion after 5 weeks of aluminum and silicon exposure is depicted in Fig. 1. Rats in the negative control group excreted a total of 197 μg/kg over the 4-day period of measurement; however, as expected, total urinary aluminum elimination by rats in the positive control group was significantly greater: 1,619 μg/kg. This value was about 2–3 times higher than the mean aluminum levels found in the urine of the groups supplemented with 59 and 118 mg Si/L in drinking water, respectively.

**DISCUSSION**

The decreased tissue aluminum concentrations found in the silicon-exposed groups show that dietary silicon supplementation effectively prevents the gastrointestinal absorption of aluminum. The marked reduction in the levels of aluminum excreted into urine, the route of aluminum elimination (Domingo et al., 1991, 1994), would also corroborate this finding. Moreover, in most

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**TABLE 1.** Aluminum concentrations in various tissues of rats concurrently exposed to aluminum and silicon for 5 weeks

<table>
<thead>
<tr>
<th></th>
<th>Brain</th>
<th>Liver</th>
<th>Bone</th>
<th>Spleen</th>
<th>Kidney</th>
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<tbody>
<tr>
<td><strong>Negative control</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>−Al, −Si</td>
<td>ND</td>
<td>0.78 ± 0.69</td>
<td>8.95 ± 2.90</td>
<td>3.24 ± 3.89</td>
<td>1.38 ± 1.31</td>
</tr>
<tr>
<td><strong>Positive control</strong></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>+Al, −Si</td>
<td>1.14 ± 0.53</td>
<td>4.39 ± 1.56</td>
<td>16.30 ± 4.95</td>
<td>6.77 ± 2.03</td>
<td>3.33 ± 3.05</td>
</tr>
<tr>
<td>+Al, +Si (59 mg/L)</td>
<td>ND</td>
<td>0.14 ± 0.38</td>
<td>4.54 ± 1.15</td>
<td>0.29 ± 0.40</td>
<td>1.24 ± 0.48</td>
</tr>
<tr>
<td>+Al, +Si (118 mg/L)</td>
<td>ND</td>
<td>0.96 ± 0.14</td>
<td>1.46 ± 0.61</td>
<td>0.46 ± 0.57</td>
<td>0.45 ± 0.51</td>
</tr>
</tbody>
</table>

Results are presented as milligrams per gram of tissue wet weight and are expressed as mean ± SD. ND, not detected. Detection limit = 0.001 μg/g.

* p < 0.05, ** p < 0.01, *** p < 0.001; significantly different from negative control group.

* p < 0.01, ** p < 0.001; significantly different from positive control group.

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**TABLE 2.** Aluminum concentrations in different cerebral regions of rats concurrently exposed to aluminum and silicon for 5 weeks

<table>
<thead>
<tr>
<th></th>
<th>Cortex</th>
<th>Hippocampus</th>
<th>Striatum</th>
<th>Cerebellum</th>
<th>Thalamus</th>
<th>Olfactory bulb</th>
<th>Rhachidical bulb</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative control</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>−Al, −Si</td>
<td>3.98 ± 3.38</td>
<td>2.42 ± 4.33</td>
<td>7.12 ± 5.18</td>
<td>11.01 ± 5.39</td>
<td>7.25 ± 7.88</td>
<td>36.94 ± 35.34</td>
<td>7.51 ± 9.21</td>
</tr>
<tr>
<td><strong>Positive control</strong></td>
<td></td>
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<tr>
<td>+Al, −Si</td>
<td>57.18 ± 18.87</td>
<td>17.08 ± 10.34</td>
<td>15.82 ± 8.58</td>
<td>62.13 ± 11.69</td>
<td>41.58 ± 35.22</td>
<td>124.30 ± 109.78</td>
<td>110.80 ± 68.47</td>
</tr>
<tr>
<td>+Al, +Si (59 mg/L)</td>
<td>1.56 ± 2.69</td>
<td>ND</td>
<td>1.93 ± 3.84</td>
<td>12.02 ± 14.52</td>
<td>2.96 ± 4.95</td>
<td>24.59 ± 20.03</td>
<td>9.34 ± 8.23</td>
</tr>
<tr>
<td>+Al, +Si (118 mg/L)</td>
<td>1.09 ± 0.91</td>
<td>1.32 ± 1.07</td>
<td>1.16 ± 1.41</td>
<td>2.01 ± 2.36</td>
<td>0.74 ± 0.43</td>
<td>0.96 ± 1.93</td>
<td>3.57 ± 4.18</td>
</tr>
</tbody>
</table>

Results are presented as micrograms per gram tissue wet weight and are expressed as mean ± SD. ND, not detected. Detection limit = 0.001 μg/g.

* p < 0.05, ** p < 0.01, *** p < 0.001; significantly different from negative control group.

* p < 0.05, ** p < 0.01, *** p < 0.001; significantly different from positive control group.
tissues of silicon-supplemented rats, aluminum concentrations were even lower than the levels found in the rats from the negative control group (−Al, −Si), which were exposed only to environmental aluminum and did not receive oral aluminum.

The effect of silicon is due to a “sequestration” of the metal, which reduces its effect on enzymic and Mg²⁺-dependent processes and promotes aluminum excretion and reduces tissue aluminum accumulation (Birchall, 1992). Because silicic acid is a very weak acid, it interacts only with metals that are basic. Thus, the only relevant metals that are basic at physiological pH are aluminum and ferric iron. Although the interaction of silicic acid with ferric iron is weak, the strong and specific interaction with aluminum suggests the protective role of silicon (Birchall, 1992; Petersen et al., 1992).

In the current study, silicon administration reduced the aluminum concentration in the olfactory bulb, the cerebellum, and the rachidical bulb, with the cerebral regions showing the greatest aluminum accumulation in both the negative and positive control groups. This agrees with the results of a recent investigation on the age-related effects of aluminum ingestion on brain aluminum accumulation and behavior in rats, which show that the olfactory bulb is the cerebral region with the highest aluminum level (Domingo et al., 1996). The olfactory-related areas of the brain have been invariably and severely involved in AD, in contrast to the minimal changes in the somatosensory and primary visual brain areas (Esiri and Wilcock, 1984; Roberts, 1986).

Because the olfactory system is the only portion of the central nervous system with exposure to the external environment, aluminum may reach this system through the olfactory pathways (Roberts, 1986; Perl and Good, 1991). Consequently, the present finding of high aluminum concentrations in the olfactory bulb of rats would be in agreement with the hypothesis that AD may begin in the nose and be caused by aluminosilicates (Roberts, 1986; Perl and Good, 1991). These compounds have been found in senile plaques of patients with AD (Candy et al., 1986; Good and Perl, 1993).

However, because AD is considered to be a heterogeneous disorder, it is important to consider the role of environmental factors such as aluminum exposure in its molecular pathogenesis (Harrington et al., 1994; McLachlan, 1995; McLachlan et al., 1996; Savory et al., 1996). With regard to that hypothesis, the possible use of silicates as a therapeutic agent for AD was recently suggested (Fisman et al., 1995). Silicates could be effective in reducing the Al³⁺ concentrations in circulating blood, and thus aluminum would be less available to cross the blood-brain barrier (Fisman and Moore, 1994; Fisman et al., 1995).

The chemical affinity of silicic acid for aluminum has been shown to reduce the bioavailability of aluminum in studies of human gastrointestinal absorption (Bellia et al., 1996), and it has also been reported that silicic acid protects against aluminum toxicity in biota by probable formation of hydroxyaluminosilicates (Birchall et al., 1989; Exley and Birchall, 1993). The results of the present study in rats corroborate the beneficial effects of dietary silicon in reducing the aluminum body burden, including brain aluminum concentrations. Thus, dietary silicon supplementation could be of therapeutic value to prevent the chronic aluminum accumulation in the brain.

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**REFERENCES**


