González-Muñoz, M.J., Peña, A. and Meseguer, I. (2008) 'Role of beer as a possible protective factor in preventing Alzheimer's disease', Food and chemical toxicology, 46(1), pp. 49–56.

Role of beer as a possible protective factor in preventing Alzheimer's disease

M.J. González-Muñoz *, A. Peña, I. Meseguer

Department of Nutrition, Bromatology and Toxicology, Pharmacy School, University of Alcalá, Crta. Madrid-Barcelona, Km 33.6, 28871 Alcalá de Henares, Madrid, Spain

Abstract

Aluminium (Al), a neurotoxin, has lately been implicated as one of the possible causal factors contributing to Alzheimer's disease. Because silicon (Si) intake can affect the bioavailability of aluminium, the object of the present study was to assess whether moderate beer consumption might, as a source of dietary Si, affect the toxicokinetics of Al and thereby limit that element's neurotoxicity.

The results obtained confirmed that at moderately high levels of beer intake the Si present in the beer was able to reduce Al uptake in the digestive tract and thus was able to slow the accumulation of this metal in the body, brain tissue included.

In consequence, moderate beer consumption, due to its content in bioavailability silicon, possibly affording a protective factor for preventing Alzheimer's disease, could perhaps be taken into account as a component of the dietary habits of the population.

1. Introduction

The neurodegenerative disorder known as Alzheimer's disease is the most common cause of dementia in the elderly and is the fourth leading cause of death in the developed countries (Guimera` et al., 2002; Smorgon et al., 2004). The number of cases of this disease is expected to quadruple worldwide by the year 2047 (Luchsinger and Mayeux, 2004; Mattson, 2004).

The etiopathogenesis of Alzheimer's disease is unknown, but it seems clear that environmental factors working in conjunction with a genetic propensity are likely to play a major role in the onset of this disorder. Some workers have pointed to aluminium as a possible factor contributing to the development of this disease (Domingo, 2000; Rondeau, 2002), in as much as this metal is conducive to oxidative stress in the brain, and oxidative damage is the primary risk factor for Alzheimer's disease and other neurodegenerative disorders (Matsuzaki et al., 2004).

Although highly controversial, the hypothesis of a link between Al in drinking water and Alzheimer's disease has been supported by several epidemiological studies (Ron-deau et al., 2006). Perl and Moalem (2006) believe that this highly reactive element, known to cross-link hyperphosphorylated proteins, may play an active role in the pathogenesis of critical neuropathology lesion in Alzheimer's disease and the other related disorders.

The widespread use of products made from or containing Al is ensuring the presence of Al in our bodies. It is the most abundant metallic element in the Earth's crust, the third most abundant element overall and has been described as omnipresent as it can be found in measurable quantities in food, soil, water and air. Despite being present at trace levels in almost vegetation and animals, even small elevation in the concentration of Al can have deleterious effects (Perry and Keeling-Tucker, 1998).

Aluminum's toxicity in human beings is a well-established fact (Domingo, 2000; Becaria et al., 2002), and it is a highly toxic metal even at low levels of exposure (Perry and Keeling-Tucker, 1998). The brain is the target organ, hence this element acts principally as a neurotoxin (Exley, 1999; Yokel et al., 1999), though it is also known to affect the bones and the red blood cells (Jarava et al., 2001; Pe´rez- Granados and Vaquero, 2002). Al causes the accumulation of tau protein and amyloid-beta protein in experimental animals and induces neural apoptosis in vivo as well as in vitro (Kawahara, 2005). Al accumulation in the tangle- bearing neurons is the case of amylotrophic lateral sclerosis/parkinsonism-dementia complex of Guam (Perl and Moalem, 2006).

Because gastrointestinal uptake of aluminium in healthy individuals is slow and excretion in the urine, the main excretory route (Pe´rez-Granados and Vaquero, 2002; Yokel, 2000), is fast, the deleterious effects of Al on health, though inexorable, will be low at normal levels of exposure (Popplewell et al., 1998; Baydar et al., 2003).

At the same time, it has been suggested that silicon and silicic acid may decrease the bioavailability of aluminium by blocking uptake through the gastrointestinal tract (Parry et al., 1998) and by impeding reabsorption in the kidneys (Reffitt et al., 1999).

Bioavailable silicon, that is, silicon in the form of silicic acid or orthosilicic acid, is mainly found in foods rich in fibre and whole grains, with beer being one of the main sources of this element in the diet (Bellia et al., 1994; Jugdaohsingh et al., 2002; Sripanyakorn et al., 2004).

The present study has examined the effect of beer con- sumption as a source of silicon on the bioavailability of aluminium and the possible role of beer consumption in averting aluminium's neurotoxicity.

A previous paper (Peña et al., 2006) demonstrated that beer intake did, as postulated, exert an effect on the kinetics of aluminium uptake and excretion. In the earlier three-day study, male rats were subjected to acute exposure to aluminium (450 lg/ml), while being given two types of beer, i.e., alcoholic and non-alcoholic beer, to drink at two intake levels, one equivalent to moderate to low consump- tion in humans (0.5 l/d) and another equivalent to moder- ate to high consumption in humans (1 l/d).

Following this verification, in the earlier study, of the postulated influence of beer consumption and demonstration of the type and amount of beer that produced the greatest effect, the present experiment consisted of a longer-term study intended to substantiate the possible protective action of beer against chronic exposure and establish its role in the accumulation of aluminium in brain tissue.

2. Materials and methods

2.1. Animals and experimental protocol

The protocol employed in this experiment was approved by Spain's Commission for Science and Technology and by an internal School of Pharmacy review board at the University of Alcala´ (Spain).

Male NMRI mice (Animal Research Centre, University of Alcala´) weighing approximately 30 g each were divided into four groups (n = 12).

Three of the groups received aluminium nitrate, Al(NO3)3 Æ 9H2O (Aldrich CAS 7784-27-2), in their drinking water (450 lg/ml) for 3 months, the same dose range used by different authors in similar studies (Seaborn and

Nielsen, 1994; Belles et al., 2001; Granero et al., 2004). The solutions were prepared dairy and the content of Al was measured in each batch.

Mice in the first of these groups were also administered by gavage

2.5 ml of a commercial beer (5.5% volume) per week (given daily at equally divided dose), while mice in the second group received by gavage 2.5 ml if a solution of silicic acid (Fluka Chemie, Buchs, Switzerland) per week (given daily at equally divided doses), at a concentration of 50 mg Si/l. The silicic acid solution is approximately twice the Si content of the beer in order to check the influence of the concentration on the possible beneficial effect of this element. The third group received neither beer nor Si (positive control group), and the fourth group received distilled water and was used as the negative control. The mice were housed in an animal room under standard conditions of temperature (21 ± 1 ºC) and humidity (55 ± 10%), with a 12-h light/12-h dark cycle.

At the end of the treatment period, the mice were transferred to individual plastic metabolic cages, and the urine and faeces were collected (24 h) for Al and Si analysis. The animals were then sacrificed by piercing the heart, being anesthetized using halothane, and blood and brain tissue samples were taken for subsequent analysis. The blood collected per mouse was approximately 2 ml was kept in polyethylene tube with heparin. The brain was divided equally in two parts. Whole right hemibrain was used to reach the mineral content, while the left hemibrain was kept in formaldehyde in order to realize the histological study.

During the all experiment (3 months), the animals were trained in the rotarod wheel, in order to evaluate the possible cerebral damage, coordination and fatigue resistance.

2.2. Analytical methods

The Al and Si contents of the beer were determined in a number of samples, after which levels of these two mineral elements in the faeces, urine, and blood were also determined.

The Si content was measured by means inductively coupled plasma atomic emission spectrometry ICP-OES (Perkin–Elmer Optima model 3200 RL) using the emission lines of Si 254.611 nm and 212.412 nm. The Al measure was carried out by two different techniques, depending on the level: for faeces samples, Al was determined by the same equipment using for Si (ICP-OES), although the emission line was, in this case, 308.215 nm. The level of Al in rest of the matrix (urine, serum and brains) was measured by means of inductively coupled plasma mass spectrometry (Perkin–Elmer Elan model 6000, ICP-MS), using the only one isotope of Al27. The used emission lines and isotopes are free of spectral interferences in these matrix types.

The Al content was measured by means of inductively coupled plasma mass spectrometry (Perkin–Elmer Elan model 6000, ICP-MS), and the Si content was measured by means of inductively coupled plasma atomic emission spectrometry model Poly Sca G1E, ICP-AES following wet ashing of the organic matter according to the method proposed by Granero et al. (2004). Each sample (2.5 ml) was digested with 2 ml of 65% nitric acid (Suprapur, Merck, Darmstad, Germany) in Teflon bombs for 8 h at room temperature, and subsequently heated at 100 ºC for 12 h. After cooling, solutions were filtered and made up to 25 ml with deionised water. The accuracy of the instrumental methods was validated by replicating all samples as well as by taking measurements of reference material (lobster hepatopancreas, NRC Canada TORT 2) every 10 samples. Quantification was based on the most abundant isotope of each element free of analytical interferences. The mean recovery rates were between 90% and 95%.

2.3. Histological techniques

In a general histological study, in order to evaluated a possible damage cerebral, samples of brain tissue from the negative controls and the Al- dosed animals were examined by light microscopy after fixing in paraffin and staining with haematoxylin and eosin to establish possible brain damage produced by the Al. Previously, the brains were dehydrated by upward gradation alcohol solutions and, subsequently, the alcohol were removed and substituted by xylene.

2.4 Statistical Analysis

The statistical significance of the data was computed by one-way analysis of variance (ANOVA). The Kolmogorov–Smirnov test was used to confirm that the values were normally distributed, while homogeneity of the variances was assessed using Snedecor’s F-test. In addition, the LSD multiple rank test was used to determine which means differed significantly from the others, using a significance level of 0.05% or less.

3. Results

The Al and Si contents of the beer employed in this study were determined before first administering the beer to the test animals. The Al concentration was 0.40 ± 0.12 lg/g, and the

Si concentration was 24.56 ± 2.45 lg/g. The Al content of the beer was thus very low in comparison with the experimental concentration to which the animals were exposed, 450 lg Al/ml.

Fig. 1 depicts the growth curves obtained for the positive and negative control animals and for the mice dosed with Al and fed beer or silicon.

The growth curves indicate similar growth rates for all four test groups without any significant differences between the groups.

The animals in all the groups gained weight as the study advanced, with the weight gain levelling off in the final weeks of the trial. The weights recorded fell within the range of weights for these mice (IFFA CREDO) specified by Charles River Laboratories, Inc.

The neural damage of animals was determined by the number of downfalls in 45 min of running in the rota-rod wheel. The results obtained show not significant differences between groups, suggesting any change in the behaviour of the treated animals.

3.1. Faecal excretion

The mice administered silicic acid excreted significantly ($p < 0.001$) more Al than the Al-dosed positive controls (665.87 vs. 487.38 lg/g, Table 1). This same effect ($p < 0.05$) was also observed on comparing faecal Al levels in the mice that were administered beer and in the positive controls dosed with Al (581.03 vs. 487.38 lg/g).

Faecal Si concentrations in the animals dosed with Al were higher than in the negative control group (123.45 vs. 93.95 lg/g). Administering beer or silicic acid brought about a non-significant increase in the faecal excretion of

Si compared with the positive and negative control groups (Table 1).

3.2. Urinary excretion

The animals dosed with Al had significantly higher urine Al levels than the negative control mice. Animals in the Si treated groups excreted slightly more Al into the urine than those in the positive group, although the difference was not significant (Table 2).

Comparing the positive control group with the negative control group, the urine Si levels (Table 2) can be seen to be non-significantly lower in the former (3.02 vs. 3.8 lg/mmol creatinine). Likewise, the urine Si concentration increased

significantly in the two Si groups.

3.3. Serum levels

A comparison of Al levels in the blood revealed no significant differences in concentrations (1.72 vs. 1.49 lg/l) in the positive and negative control mice (Table 3).

In the animals that had supplementary Si intake, blood Al levels were significantly lower ($p < 0.001$) in both the mice that were fed beer and the mice that were administered silicic acid than in the positive control group (Table 3).

respect to the mice administered Si in the form of silicic acid was not significant.

Brain Al levels were significantly lower ($p < 0.01$) in the animals administered silicic acid than in the positive con- trol mice (1.34 vs. 3.85 lg/g). Si intake in the form of beer also lowered the Al levels in the brain tissue, though not significantly (2.45 vs. 3.85 lg/g).

Brain tissue Si levels in the mice dosed with Al were sig- nificantly higher than in the negative controls (52.83 vs. 13.64 lg/g) (Table 4).

At the same time, brain Si levels in the mice exposed to Al and treated with Si were higher than in the positive con- trols (Table 4), as was only to be expected since these mice were receiving supplementary Si.

3.5. Histological study

The general histological examination revealed differences between the brains of the animals in the various

On the other hand, there was no difference in serum Al levels in the mice fed beer (0.94 lg/l) compared with the mice fed silicic acid (0.82 lg/l).

The blood Si level in the positive control group did not differ significantly from the level in the negative control mice (23.78 vs. 29.63 lg/g) but was nonetheless slightly lower in the Al-dosed animals (Table 3).

Serum Si concentrations in the mice given either beer or silicic acid were in both cases lower than in the animals in the positive control group, and the difference was significant ($p < 0.001$) in the case of the mice treated with silicic acid.

3.4. Brain tissue levels

Table 4 presents the Al concentration values for brain tissue in the different test groups. The Al levels in the brain tissue of the animals exposed to Al were significantly higher ($p < 0.01$) than the levels in the negative control mice (3.85 vs. 0.98 lg/g). The brain tissue of mammalians content between 1.1–1.9 lg Al/g (Cacabelos, 1990), so the results for no-intoxicated animal are into this range of values.

Brain tissue Al levels were lowest in the animals in the negative control group. However, the differences with groups. White matter spongiosis was observed in the positive control mice,

that is, in the animals that were exposed to Al without being given any supplementary Si by way of treatment, but no neuronal necrosis was present (Fig. 2). The brains of the Al-dosed animals treated with Si had necrosis both in the cortex and in the cerebellum (Fig. 3). In contrast, the brains of the Al-dosed animals that were fed beer exhibited necrosis of cortical neurons (Fig. 4). However, these results could not be considered concluded and should be realized a deeper study, to validate the pathologic repercussions.

4. Discussion

The results obtained here for the Al content of the beer tested fell within the range of values of 0.037–0.795 lg Al/ ml for Spanish beers published by Lo´pez et al. (1998) and were in agreement with the values of 0.49 ± 0.11 lg Al/ml (Granero et al., 2004) and 0.56 ± 0.10 lg Al/ml (Vin˜as et al., 2002) previously reported for bottled beers.

According to the US Agency for Toxic Substances and Disease Registry, the minimal risk level (MRL) for Al is

2.0 mg/kg/d (ATSDR, 2001). Consequently, consumption of 1 l of beer a day would contribute 0.29% of this MRL in a person weighing 70 kg and hence would not pose any health risk in this respect.

The Si content recorded for the beer was lower than the earlier published values of 36.8 lg/ml reported by Granero et al. (2004) and 36.0 lg/ml reported by Sendra and Carbo- nell, (1999), though it was nonetheless within the range of values of 10.1–35.0 mg Si/ml for bottled beers published by Sripanyakorn et al. (2004).

Al is basically eliminated in the urine, and thus faecal levels of this metal are the sum of the Al not taken up in the digestive tract and the Al eliminated in the bile (DeV- oto and Yokel, 1994).

In consequence, the higher faecal levels of Al in the animals that were fed beer as compared to the negative control group might be a reflection of the possible effect of beer on the toxicokinetics of Al. The Si content of the beer would be responsible for this effect, since this element is able to reduce dietary uptake of Al in the gastrointestinal tract, thereby increasing excretion in the faeces (Bellia et al., 1996).

The Si–Al interaction was most clearly observable in the animals dosed with Al and administered silicic acid. These findings are consistent with those of other workers (Bellia et al., 1996; Gra¨ske et al., 2000), who pointed to the forma- tion of aluminosilicate species like hydroxy-aluminoslicates (HAS) (Parry et al., 1998; Perry and Keeling-Tucker, 1998) as a possible mechanism for this interaction. It been shown that insoluble and biologically inert HAS species can form in solutions containing Al at near physiological levels when the pH is above 4.5. It is suggested that the mechanism by which these HAS form is the nucleation of aluminium hydroxide ant it appear the biological system may already be exploiting this reaction (Perry and Keeling-Tucker, 1998). The Si content of the beer appeared to lend itself to this same sort of interaction.

Bearing in mind that the amount of Si supplied in the form of silicic acid was greater than the amount supplied in the form of beer; this effect appears to be dependent on the amount of Si present in the lumen.

In addition, the significantly higher levels of faecal Si in the groups dosed with Al and at the same time fed beer or silicic acid as compared to the levels in the positive and negative control groups would seem to support the hypoth- esis that Al and Si combine to form compounds that are not taken up by the digestive tract. The HAS would most probably have a Si:Al ratio of 1:0 (HASB) and so, increase in Al faeces implies an increase in the Si content in faeces. Based on these findings, beer would indeed seem to exert protective action against dietary Al intake by curtailing

uptake of Al in the digestive tract.

The results for urinary excretion show that Si supple- mentation produces a slightly increase in urinary As respect to positive group. On the other hand, the presence of Al increases the content of Si in urine in a significant way. These findings could indicate that silicon appears to be important in the renal excretion of the absorbed alumin- ium. According with Roberts et al. (1998), high silicon out- put can increase the renal excretion of Al possibly by reduction in its re-absorption through formation of alumninosilicates. Further, the high urine silicon indicates that the renal re-absorption of Si is low.

Blood sample analysis yielded similar serum levels of Al in the dosed and the negative control animals. This finding is perhaps indicative of the low rate of Al uptake and the rapid delivery of Al once it has been taken up by the body (Pe´rez-Granados and Vaquero, 2002).

However, supplementary dietary Si in the form of either silicic acid or beer brought about a significant decrease in serum concentrations of Al. This could be an outcome of the interaction between Si and Al in the digestive tract. Lowe serum Al in the Si groups might also suggest higher Al deposition in tissues or more rapid excretion of Al via the kidney. Therefore, serum Al is a very poor indicator of what is happening to systemic Al.

In addition, the mice exposed to Al while being admin- istered silicic acid or beer had higher levels of both urine and faecal Si (Tables 2 and 3). This resulted in lower Si lev- els in the blood. Moreover, the low serum but high urine concentration of Si suggests that if Al and Si interact to form an excretable species they do so in the kidney lumen such that Si limits the reabsorption of Al (Bellia et al., 1996).

The brain tissue analysis results show the brain to be a target organ for Al, with chronic exposure to this metal leading to significant accumulation in the brain, and the histological study revealed white matter spongiosis in the Al-dosed animals, indicating appreciable damage to the brain. The lowest concentrations of Al in the brain tis- sue were recorded for the negative control group, that is, the group that was not dosed with Al.

Beer or silicon intake lowered Al levels in the brain com- pared with the controls that were exposed to Al. Supplementary silicic acid had a satisfactory effect, in that the mice treated with silicic acid did not exhibit any differences with respect to the unexposed mice. In contrast, there were no significant differences between the mice that were fed beer and the positive control group, indicating that expo- sure to beer did not yield the same benefit as providing sil- icon. Even so, the mean Al concentration in the beer- drinking group was lower than in the

control group exposed to Al that went untreated (Table 4). Similarly, the histological findings seemed to bear out the potential beneficial effect of Si in protecting the brain from lesions produced by Al, in that the higher the dose of Si administered, the lower the degree of damage to the brain tissue.

These findings were consistent with the faecal and urinary Al levels: the higher rate of excretion in the treated animals could be a cause of the lower accumulation of Al in the brain. Therefore, silicic acid could not only able to reduce the gastrointestinal absorption of Al but also to release and excrete Al from the body store (Bellia et al., 1996).

Based on these results, administering Si would appear to be effective in preventing Al from accumulating in the brain in mice, as reported earlier by Granero et al. (2004). These authors found a linear model to describe the relation between Al and Si in brain, since Si levels in this organ were in accordance with the level of Al detected in the different groups. The results obtained by Carlisle and Curran (1987) in a study in rats suggest that Si may be an essential element in brain and dietary silicon supplementation appeared to be protective against aluminium accumulation in aging brain.

The higher Si concentrations in the brains of the animals in the positive control group than in those of the animals in the negative control group could be due to a number of different causes. For one thing, there is evidence that Al is able to produce free radicals that cause lipid peroxidation, thereby damaging neuron membranes and increasing blood–brain barrier permeability (Tokutake, 1997; Srivast- ava and Jain, 2002) and in that way allowing more dietary Si to enter the brain tissue.

For another, Desouky et al. (2002,2003) have suggested that Si may play a specific role in the detoxification of Al, possibly by forming non-toxic aluminosilicates, which are sequestered into lysosomal granules.

The physiological function of lysosomes is to degrade waste substances within cells, e.g., aluminosilicates, which accumulate and lead to lysosome dysfunction. Lipofuscin granules are a degenerate form of lysosome ubiquitous in aged brain cells. They are more abundant in the brains of individuals suffering from senile dementia and Alzheimer's disease (Tokutake et al., 1995; Tokutake and Oyanagi, 1995; Tokutake, 1997). Several experiments have demon- strated the accumulation of Al and Si in some lipofuscin granules in the brain (Candy et al., 1992; Clauberg and Joshi, 1993; Kaneko et al., 2004; Kohila et al., 2004). Consequently, exposure to Al contributes to Si accumulation in the brain, probably as a mechanism for curtailing the neurotoxicity of Al.

5. Conclusions

Al is a potentially neurotoxic metal that is now suspected of playing a role in Alzheimer's disease and other major degenerative diseases, and in consequence exposure to all sources of this metal should be curtailed.

Thanks to the potential interaction observed between Al and Si in the digestive tract and lower concentrations of Al in the blood and brain tissue, it appears that Si in the form of silicic acid

may lower the bioavailability of Al, and hence Si should be regarded as a factor that may afford protection against Al, reducing therefore, one of the risk factor for Alzheimer's disease. These result are in agree with the epidemiology study achieved by Gillette-Guyon- net et al. (2005), who conclude that silica in drinking water may reduce the risk of development Alzheimer' disease in elderly women.

Moderate to high intake of alcoholic beer may exert the same effect. Therefore, moderate beer consumption could be included in the dietary habits of the population as a possible protective factor, an aspect that supports the recent inclusion of beer in the food guide pyramid.

However, alcoholic beverage consumption needs to be kept within certain limits depending both on gender and on age and should never be promoted as a means of increasing certain nutrients, which can be obtained from other foodstuffs in the diet.

Furthermore, excessive alcohol consumption is associ- ated with higher morbidity and mortality rates (Yuan et al., 2001), even though moderate consumption may have beneficial effects on health, as, for instance, in the case of cardiovascular disease (De Loromier, 2000) and in preventing bone resorption in humans (Rapuri et al., 2000; Tucker et al., 2001; Tunner and Sibonga, 2001).

Since certain effects of alcoholic and non-alcoholic beer observed during the earlier study of acute exposure were not significant, it would be interesting to expand the find- ings presented here by undertaking a study of chronic exposure to Al in conjunction with the consumption of non-alcoholic beer, in order to ascertain whether silicon also exerts protective action in the absence of alcohol.

In addition, in view of aluminium's role in free radical formation, there is a need to identify biomarkers of lipid peroxidation in brain tissue in order to be able to ascertain whether Si is capable of interfering with this causal mech- anism of brain damage.

References

ATSDR (Agency for Toxic Substances and Disease Registry), 2001. Minimal Risk Levels (MRLs) for Hazardous Substances.

<www.atsdr.cdc.gov/mrls.html>.

Baydar, T., Papp, A., Aydin, A., Nagymajtenyi, L., Schulz, H., Isimer, A., Sahin, G., 2003. Accumulation of aluminium in rat brain: does it lead to behavioral and electrophysiological changes? Biol. Trace Elem. Res. 92 (3), 231–244.

Becaria, A., Campbell, A., Bondy, S.C., 2002. Aluminium as a toxicant.

Toxicol. Ind. Health 18 (7), 309–320.

Belles, M., Albina, M.L., Sanchez, D.J., Corbella, J., Domingo, J.L., 2001. Effects of oral aluminium on essential trace elements metabolism during pregnancy. Biol. Trace Elem. Res. 79 (1), 67–81.

Bellia, J.P., Birchall, J.D., Roberts, N.B., 1994. Beer: a dietary source of silicon. Lancet 343, 235.

Bellia, J.P., Birchall, J.D., Roberts, N.B., 1996. The role of silicic acid in the renal excretion of aluminium. Annal. Clin. Lab. Sci. 26 (3), 227– 233.

Cacabelos, R., 1990. The neurobiology and molecular genetics of Alzheimer's disease: the diagnostic markers and therapy. Med. Clin. (Barc). 95 (13), 502–516.

Candy, J.M., McArthur, F.K., Oakley, A.E., Taylor, G.A., Chen, C.P., Mountfort, S.A., Thompson, J.E., Chalker, P.R., Bishop, H.E., Beyreuther, K., 1992. Aluminium accumulation in relation to senile plaque and neurofibrillary tangle formation in the brains of patients with renal failure. J. Neurol. Sci. 107 (2), 210–218.

Carlisle, E.M., Curran, M.J., 1987. Effect of distary silicon and aluminium in silicon and aluminium levels in rat brain. Alzheimer Dis. Assoc. Disord. 1 (2), 83–89.

Clauberg, M., Joshi, J.G., 1993. Regulation of serine protease activity by aluminium: implications for Alzheimer's disease. Proc. Natl. Acad. Sci. USA 90, 1009–1012.

De Loromier, A.A., 2000. Alcohol, wine, and health. Am. J. Surg. 180, 357–361.

Desouky, M.M., Powell, J.J., Jugdaohsingh, R., White, K.N., McCrohan, C.R., 2002. Influence of oligomeric silicic and humic acids on aluminium accumulation in a freshwater grazing invertebrate. Eco- toxicol. Environ. Safe. 53, 382–387.

Desouky, M.M., McCrohan, C.R., Jugdaohsingh, R., Powell, J.J., White, K.N., 2003. Effect of orthosilicic acid on the accumulation of trace metals by the pond snail Lymnaea stagnalis. Aquatic Toxicol. 64, 63– 71.

DeVoto, E., Yokel, R.A., 1994. The biological speciation and toxicoki- netics of aluminium. Environ. Health Perspect. 102, 940–951.

Domingo, J.L., 2000. El aluminio como possible factor etiopatoge´nico en la enfermedad de Alzheimer. Rev. Toxicol. 17, 3–11.

Exley, C., 1999. A molecular mechanism of aluminium-induced Alzhei- mer's disease? J. Inorg. Biochem. 76, 133–140.

Gillette-Guyonnet, S., Andrieu, S., Nourhashemi, F., de La Gueronniere, V., Grandjean, H., Vellas, B., 2005. Cognitive impairment and composition of drinking water in women: finding of the EPIDOS study. Am. J. Clin. Nutr. 81 (4), 897–902.

Granero, S., Vicente, M., Aguilar, V., Mart´ınez-Para, M.C., Domingo, J.L., 2004. Effects of beer as a source of dietary silicon on aluminium absorption and retention in mice. Trace Elem. Electrol. 21 (1), 28–32. Gra¨ske, A., Thuvander, A., Johannisson, A., Gadhasson, I., Schu¨ tz, A., Festin, R., Wicklund, G.A., 2000. Influence of aluminium on the immune system, an experimental study on volunteers. Biometals 13,

123–133.

Guimera`, A., Girone`s, X., Cruz-Sa´nchez, F.F., 2002. Actualizacio´n sobre la patolog´ıa de la enfermedad de Alzheimer. Rev. Esp. Patol. 35 (1), 21–48.

Jarava, C., Armas, J.R., Palma, A., 2001. Aluminio y enfermedad o´sea ure´mica. Utilidad diagno´stica del aluminio se´rico y del test de la deferoxamina (DFO). Nefrolog´ıa 21 (2), 174–181.

Jugdaohsingh, R., Anderson, S.H., Tucker, K.L., Elliott, H., Kiel, D.P., Thompson, R.P., Powell, J.J., 2002. Dietary silicon intake and absorption. Am. J. Clin. Nutr. 75, 887–893.

Kaneko, N., Yasui, H., Takada, J., Suzuki, K., Sakurai, H., 2004. Orally administered aluminum-maltolate complex enhances oxidative stress in the organs of mice. J. Inorg. Biochem. 98, 2022–2031.

Kawahara, M., 2005. Effect of aluminium on the nervous system and its possible link with neurodegenerative diseases. J. Alzheimer Dis. 8 (2), 171–182.

Kohila, T., Parkkonen, E., Ta¨hti, H., 2004. Evaluation of the effects of aluminium, ethanol and their combination on rat brain synaptosomal integral proteins in vitro and after 90-day oral exposure. Arch. Toxicol. 78, 276–282.

Lo´pez, F.F., Cabrera, C., Lorenzo, M.L., Lo´pez, M.C., 1998. Aluminium levels in wine, beer and other alcoholic beverages consumed in Spain. Sci. Total Environ. 220 (1), 1–9.

Luchsinger, J.A., Mayeux, R., 2004. Dietary factors and Alzheimer's disease. Lancet Neurol. 3 (10), 579–587.

Matsuzaki, S., Manabe, T., Katayama, T., Nishikawa, A., Yanagita, T., Okuda, H., Yasuda, Y., Miyata, S., Meshitsuka, S., Tohyama, M., 2004. Metals accelerate production of the aberrant splicing isoform of preselin-2. J. Neurochem. 88 (6), 1345–1351.

Mattson, M.P., 2004. Pathways towards and away from Alzheimer's disease. Nature 430 (7000), 631–639.

Parry, R., Plowman, D., Trevor Delves, H., Roberts, N.B., Birchall, J.D., Bellia, J.P., Davenport, A., Ahmad, R., Fahal, I., Altmann, P., 1998. Silicon and aluminium interactions in haemodialysis patients. Nephrol. Dial. Transplant 13, 1759–1762.

Pen˜a, A., Meseguer, I., Gonza´lez, M.J., 2006. Posible efecto protector de la cerveza sobre la toxicidad del aluminio. Rev. Toxicol. 22 (Suppl. 1) http://tox.umh.es/aetox/index.htm.

Pe´rez-Granados, A.M., Vaquero, M.P., 2002. Silicon, aluminium, arsenic and lithium: essentiality and human health implications. J. Nutr. Health Aging 2, 154–162.

Perl, D.P., Moalem, S., 2006. Aluminium and Alzheimer's disease, a personal perspective after 25 years. J. Alzheimer Dis. 9 (Suppl. 3), 291–

300.

Perry, C.C., Keeling-Tucker, T., 1998. Aspects of the bioinorganic chemistry of silicon in conjunction with the biometals calcium, iron and aluminium. J. Inorg. Biochem. 69, 181–191.

Popplewell, J.F., King, S.J., Day, J.P., Ackrill, P., Fifield, L.K., Cresswell, R.G., di Tada, M.L., Liu, K., 1998. Kinetics of uptake and elimination of silicic acid by a human subject: a novel application of 32Si and accelerator mass spectrometry. J. Inorg. Biochem. 69, 177–180.

Rapuri, P.B., Gallagher, J.C., Balhorn, K.E., Ryschon, K.L., 2000. Alcohol intake and metabolism in elderly women. Am. J. Clin. Nutr. 72, 1206–1213.

Reffitt, D.M., Jugdaohsingh, R., Thompson, R.P., Powell, J.J., Hampson, G.N., 1999. Silicic acid: its gastrointestinal uptake and urinary excretion in men and effects on aluminium excretion. Inorg. Biochem. 76 (2), 141–147.

Roberts, N.B., Clough, A., Bellia, J.P., Kim, J.Y., 1998. Increased absorption of aluminium from a normal dietary intake in dementia. J. Inorg. Biochem. 69 (3), 171–176.

Rondeau, V., 2002. A review of epidemiologic studies on aluminium and silicon in relation to Alzheimer's disease and associated disorders. Rev. Environ. Health 17 (2), 107–121.

Rondeau, V., Iron, A., Letenneur, L., Commenges, D., Duchene, F., Arveiler, B., Dartigues, J.F., 2006. Analysis of the effect of aluminium in drinking water and transferrin C2 allele on Alzheimer's disease. Eur.

J. Neurol. 13 (9), 1022–1025.

Seaborn, C.C., Nielsen, F.H., 1994. High dietary aluminium affects the response of rats to silicon deprivation. Biol. Trace Elem. Res. 41 (3), 295–304.

Sendra, J.M., Carbonell, J.V., 1999. Evaluacio´n de las propiedades nutritivas, funcionales y sanitarias de la cerveza, en comparacio´n con otras bebidas. Centro Informacio´n Cerveza y Salud (Eds).

Smorgon, C., Mari, E., Atti, A.R., Dalla Nora, E., Zamboni, P.F., Calzoni, F., Passaro, A., Fellin, R., 2004. Trace elements and cognitive impairment: an elderly cohort study. Arch. Gerontol. Geriatr. (Suppl. 9), 393–402.

Sripanyakorn, S., Jugdaohsingh, R., Elliott, H., Walker, C., Mehta, P., Shoukru, S., Thompson, R.P., Powell, J.J., 2004. The silicon content of beer and its bioavailability in healthy volunteers. Br. J. Nutr. 91, 403– 409.

Srivastava, R.A.K., Jain, J.C., 2002. Scavenger receptor class B type I expression and elemental analysis in cerebellum and parietal cortex regions of the Alzheimer's diseased brain. J. Neurol. Sci. 196, 45–52.

Tokutake, S., 1997. Accumulation of aluminium and silicon in lipofuscin granules suggests retardation of the blood-brain barrier function by aging. Ann. NY Acad. Sci. 826, 510–512.

Tokutake, S., Oyanagi, S., 1995. Accumulation of aluminium and silicon in lipofuscin granules. Gerontol 41, 131–142.

Tokutake, S., Nagase, H., Morisaki, S., Oyanagi, S., 1995. Aluminium detected in senile plaques and neurofibrillary tangles is contained in lipofuscin granules with silicon, probably as aluminosilicate. Neurosci. Lett. 185 (2), 99–102.

Tucker, K.L., Kiel, D.P., Powell, J.J., Qiao, N., Hannan, M.T., Jugdaohsingh, R., 2001. Dietary silicon and bone mineral density: the Framingham Study. J. Bone Miner. Res. 16 (Suppl. 1), S510.

Tunner, RT., Sibonga, J.D., 2001. Effects of alcohol use and estrogen on bone. Alcohol Res. Health 25, 276–281.

Vin˜as, P., Aguinaga, N., Lo´pez-Garc´ıa, I., Herna´ndez-Co´rdoba, M., 2002. Determination of cadmium, aluminium, and copper in beer and products used in its manufacture by electrothermal atomic absorption spectrometry. J. AOAC Int. 87 (3), 736–743.

Yokel, R.A., 2000. The toxicology of aluminium in the brain: a review.

Neurotoxicology 21 (5), 813–828.

Yokel, R.A., Allen, D.D., Ackley, D.C., 1999. The distribution of aluminium into and out of the brain. J. Inorg. Biochem. 76, 127– 132.

Yuan, Z., Dawdon, N., Cooper, G.S., Einstadter, D., Cebul, R., Rimm, A.A., 2001. Effects of alcohol-related disease on hip fracture and mortality: a retrospective cohort study of hospitalized Medicare beneficiaries. Am. J. Public Health 91, 1089–1093.