Aluminium and the pathogenesis of senile plaques: studies in Alzheimer's disease and chronic renal failure

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Abstract

Aluminium and silicon are co-localised as aluminosilicate at the centre of the senile plaque core. These focal deposits appear to be a consistent and specific feature associated with A4 amyloid fibrils in the plaque core and are not associated with other types of amyloidosis. A pathogenic role for Al and Si is suggested by the finding of A4 amyloid deposits, immature senile plaques and an abnormal content and distribution of these elements in the brains of patients (<55 years) with chronic renal failure. Evidence suggests that Al uptake and distribution within the brain is mediated by transferrin. The distribution of transferrin receptors may account for the vulnerability of regions such as the hippocampus and cortex which are selectively involved in Alzheimer's disease.

Senile plaques, together with neurofibrillary tangles, constitute the diagnostic neuropathological lesions of Alzheimer's disease. Plaques occur in vast numbers in the cerebral cortex and plaque densities have been shown to correlate with both the severity of cognitive impairment and the loss of cholinergic biochemical markers. They consist of dystrophic neuronal and glial processes and occur in three forms which, it has been suggested, may represent a developmental sequence (Terry and Wisniewski, 1970). "Immature" plaques are associated with loose aggregates of extracellular amyloid fibrils, while in the "mature" plaque there is a dense central core of compact amyloid. So-called "burned-out" plaques consist solely of the dense amyloid core. The amyloid fibrils consist of polymeric aggregates of a 42 amino-acid polypeptide (the A4 or β-amyloid protein) which is derived from a large glycoprotein precursor (Kang et al., 1987; Ponte et al., 1988; Tanzi et al., 1988; Kitaguchi et al., 1988). The gene for the A4 precursor is located on chromosome 21 (Kang et al., 1987), a finding of interest because Alzheimer type neuropathological changes invariably occur in Down's syndrome by the age of 40-50 years. Abnormal expression or proteolysis of the A4 precursor is thus likely to be a key stage in the cellular pathology of Alzheimer's disease although the mechanism responsible for these amyloid deposits is not understood.

Senile plaques are roughly spherical in shape. The neuritic processes which surround the plaque core are derived from several types of neurone, including processes of the diffuse cholinergic projection from the basal forebrain. As Selkoe (1987) and others have pointed out, such findings suggest a model in which diffusion of a neuritotoxic factor from a point-source could lead to pathophysiological changes in the surrounding neuropil and the involvement of glial cells. Thus, it is of considerable interest that the senile plaque core contains another major component, in addition to the A4 amyloid fibrils. Using electron- and proton-microprobe X-ray microanalysis we have shown that aluminium and silicon are present as a consistent feature of isolated and in situ senile plaque cores, in Alzheimer's disease and Down's syndrome, as well as in intellectually normal, elderly cases where these lesions also occur, albeit at much lower densities (Candy et al., 1984; Candy et al., 1985; Candy et al., 1986a; Edwardson et al., 1986). Solid-state $^{27}$Al nuclear magnetic resonance spectroscopy showed Al and Si to be present as amorphous aluminosilicates. The focal deposition of this material at the centre of the plaque core contrasts with the more diffuse distribution of other inorganic constituents, and suggests that Al and Si, or an aluminosilicate may be involved in the initiation or early stages of senile plaque formation.

Do the inorganic components have a pathogenic role or is their deposition purely secondary and non-injurious? The temporal relationship between deposition of the aluminosilicate and amyloid components of the senile plaque cores is clearly a crucial issue. A possible pathogenic role is suggested not only by the spatial distribution of Al and Si at the centre of the core but also by the apparent specificity of this association. Preliminary observations using electron microprobe X-ray microanalysis indicate that such aluminosilicate deposits are not a feature of other forms of cerebral amyloid (congophilic angiopathy and scrapie), or systemic amyloidoses (light chain IgG or serum amyloid A protein) or other neuropathological features such as Pick bodies (Perry et al., 1985) or corpora amylacea. (Candy et al., 1988). While Masters et al. (1985) also reported the
presence of aluminium and silicon in isolated senile plaque cores from Alzheimer’s disease using X-ray microanalyis, another group has claimed to be unable to find Al or Si associated with senile plaque cores using laser microprobe mass analysis, (Stem et al., 1986). We have subsequently analysed material supplied by this latter group using imaging secondary ion mass spectrometry and shown these elements to be present (Candy, Oakley and Selkoe, unpublished data). Thus it appears that aluminosilicate deposits are a consistent feature of the senile plaque core.

We have recently investigated the brains of patients who had received chronic renal dialysis, a condition in which blood levels of Al are raised as a result both of therapy with Al-containing phosphate binders and impaired renal excretion. Blood levels of Si are also elevated in this group of patients (Mauras et al., 1980). Silver staining of the cerebral cortex showed the presence of "immature" senile plaques in five out of 10 brains, including high densities in three cases at an age (49-55 years) when such features do not usually occur, except in presenile Alzheimer’s disease and Down’s syndrome. Tangles were not present in the dialysis cases. Electron microscopy revealed that the silver staining was associated mainly with extracellular clumps of amyloid fibrils. In a collaborative study with K. Beyreuther and C. Masters, antibodies raised against the synthetic 1-42 A4 amyloid protein showed immunostaining of these immature plaques. Atomic absorption spectrometry and inductively coupled plasma mass spectroscopy revealed a selective increase in Al and Si levels in the frontal cortex of the dialysis group. Imaging secondary ion mass spectroscopy revealed a cortical laminar distribution of Al consistent with intra-neuronal accumulation in dialysis cases both with and without plaques. Focal low-level deposits of Si were associated with the plaques and while Al was not detectable, it seems very likely on chemical grounds that Al contributes to the seeding of Si rich deposits. X-ray microanalysis has also shown occasional deposits of co-localised Al and Si, similar to those seen in senile plaque cores. These observations strengthen the hypothesis that Al and Si may have a pathogenic role in the deposition of A4 amyloid protein and the formation of senile plaques. Patients on chronic haemodialysis for renal failure in some cases show cerebral atrophy (Savazzi et al., 1985) and cognitive impairment (Jackson et al., 1987) which have both been related to oral intake of Al(OH)3. The relationship between such changes and the A4 amyloid deposition seen in the present study remain to be determined.

Our recent studies (Candy et al., 1987) on the mechanisms of Al uptake by the brain suggest a possible explanation for the selective vulnerability of regions such as cortex and hippocampus where the highest densities of senile plaques occur. In the absence of a suitable isotope of Al, we have used 67Ga which like Al is bound almost exclusively to transferrin in plasma. The cerebral capillary permeability of 67Ga injected systemically was consistent with a slow, protein carrier-mediated uptake. Autoradiographs showed a striking correlation between the distribution of 67Ga, which was highest in cortex, hippocampus, septum and amygdala, and the distribution of transferrin receptors which is also most dense in these areas. It is possible that the selective vulnerability of the regions affected in Alzheimer’s disease may be partly determined by Al entering the brain via the iron-transport system. Such a view is further supported by our studies using a scanning proton microprobe which indicate that small focal deposits of Fe also occur in senile plaque cores, consistent with transferrin-mediated transport of metal ions, to the site of deposition (Candy et al., 1986b).

Two major objections to the original hypothesis that Al may have a pathogenic role in Alzheimer’s disease were the apparent failure to confirm a significant increase in the gross Al content of the brain in this disorder, and the suggestion that rather there is non-specific, age-related increase in brain levels of this metal (McDermott et al., 1979). In fact, neither of these have been resolved in a definitive manner. Thus, a recent report on elemental levels in Alzheimer’s disease employing neutron activation analysis claims a 15 fold increase in Al in cortical Alzheimer samples compared with age-matched controls (Ward and Mason, 1987). Furthermore, recent work from this Unit indicates that the increase in brain Al content which is found in elderly individuals correlates with the severity of age-related neuropathological changes (plaques and tangles) and not with age per se. (McDermott and Edwardson, unpublished data). In addition, cell death could lead to the extracellular deposition of Al. Other findings consistent with the "aluminium hypothesis" include the report that in Alzheimer’s disease the Al content of neurofibrillary tangle-bearing neurones is increased (Perl and Brody, 1980). While the precise nature of the paired helical filaments which form the tangles in man has not been established, it is known that these are decorated with abnormally phosphorylated neurofilament proteins (Sternberger et al., 1985; Miller et al., 1986). Aluminium-induced tangles in susceptible species such as the rabbit are also immunostained by antibodies which recognise phosphorylated neurofilament epitopes (Troncoso et al., 1985; Munoz-Garcia et al., 1986).

Aluminium has been shown in vitro to have a considerable range of interactions with cellular constituents, which would lead to pathological changes. These include effects on gene expression; actions on calcium dependent enzymes and calcium-buffering proteins; enhancement of Fe induced free radical formation; effects on membrane fluidity; binding to phosphate groups on ATP and inositol triphosphate; impaired cytoskeletal assembly. Also, Birchall and Chappell, (1988) have drawn attention to the possible interactions between silicic acid, Si(OH)4, which is a normal constituent of plasma, and Al under physiological conditions, with the formation of insoluble aluminate species at pH 7.4. Any one or more of the above interactions could, with prolonged exposure, lead to pathophysiological changes and neuronal cell death. Such a hypothesis is not incompatible with recent evidence which shows that some familial forms of Alzheimer’s disease are due to a gene defect on chromosome 21 (St George-Hyslop et al., 1987). Involvement of genetic factors in the pathogenesis of Al-mediated dialysis...