韓國心理學會誌 : 生物 및 生理
Korean Journal of Biological and Physiological Psychology
1990. Vol. 2, 94-99

Aluminium Induced Distant Lesions in Rats - A Descriptive Anatomical Study -

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The role of aluminium as a neurotoxic agent has been demonstrated in many independent investigations. In our study, chronic intoxication of the rat CNS produced by epidural application of an aluminium salt led to neuronal degeneration of tissue distal to the primary lesion. Furthermore, the alterations seem to be restricted to distinct populations of neurons. Preliminary neuropathological data are reported.
Keyworks: rat - aluminium - chronic intoxication - distant lesions neuronal degeneration

Intorduction

It has been postulated that aluminium plays a role in the pathogenesis of several human neurological disorders such as Alzheimer's disease, Dialysis dementia, amyotrophic lateral sclerosis and Parkinson's disease (Garruto & Yase, 1986). These primary neurodegenerative conditions mostly occuring in the late adult life are linked by neurofibrillary degeneration in the presence of elevated aluminium levels (Perl, Gajdusek, Garruto, Yanagihara, & Gibbs, 1982). Furthermore this metal - in complex with silicone and aluminium silicate - appears to form the insoluble residue of both amyloid of senile plaques and neurofibrillary tangles (Perl & Brody, 1980).

But to date, its role in the pathogenesis of these disorders still remains to be determined. Animal models based on direct application of aluminium compounds in susceptible species show this type of intoxication to produce accumulations of neurofilaments in the soma of distinct populations of neurons (Kowall, Pendlebury, Kessler, Perl, & Beal, 1989). In our study, epidural cortical application of Aluminium chloride powder (ALCL3) on rat brain produced secondary lesions restricted to thalamic and hippocampal subpopulations of neurons.

Materials And Methods

Aluminium intoxication

Eight adult sprague - Dawley rats were used for histological study. The aluminium chloride powder was applied epidurally after removing a small piece of the skull 4.0㎜ posterior and 2.5㎜ dexterlateral from bregma. Rats were given an anaesthetic dose of 0.05㎖ xylocaine combined with 0.3㎖ of ketamine.

Each animal received a dose of 10mg AlCl3 power. After replacement of the removed skull the incision was sutured.

Perfusion and tissue processing

After 3 weeks the rats were anaesthetized, perfused intracardially with a 10% saline prewash followed by formaline. The removed brains were embedded in paraffin and processed for conventional histology. The 12 μm tissue sections were floated on distilled water, and transferred to autoclaved, gelatine dipped glass microscope slides. Hematoxylin and eosine staining was used for light microscopic analysis; three brains from control animals were processed in the same manner.

Results

1. Primary Lesion

A local cyst (fig. 1) developed at the site of application, affecting the adjacent tissue at certain contiguous sites, extending ipsilaterally from anterior 9000 μm to posterior 5400 μm and reaching at the posterior 3900 μm level its subcortical maximum penetrating all cortical laminae(Fig. 1).

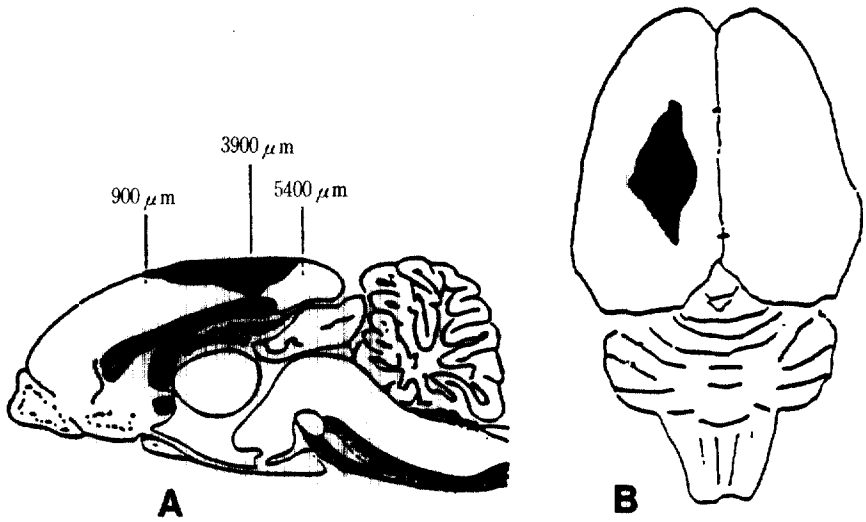

Fig.1 shows the sagittal (A) and cranial (B) extension of the primary lesion schematically.

2. Superior Cortex and Hippocampus

Within the cystic zone all neocortical laminae showed marked gliosis. In animal 1E the primary lesion at the posterior 3900 μm level reached the dorsal pyramidal cell layers of the superior hippocampus. Together with the large pyramidal cells of the subiculum which is located between the retrosplenial cortex and hippocampus, these cell populations - although non contiguous with the primary lesion site - show to be selectively affected from the aluminium application(Fig. 2)

3. CA4 - region, dentate gyrus and subiculum

In contrast to the CA1 - region there were no notable discontinuities neither in the CA4 - region, nor did the dentate gyrus show signs of degenera-

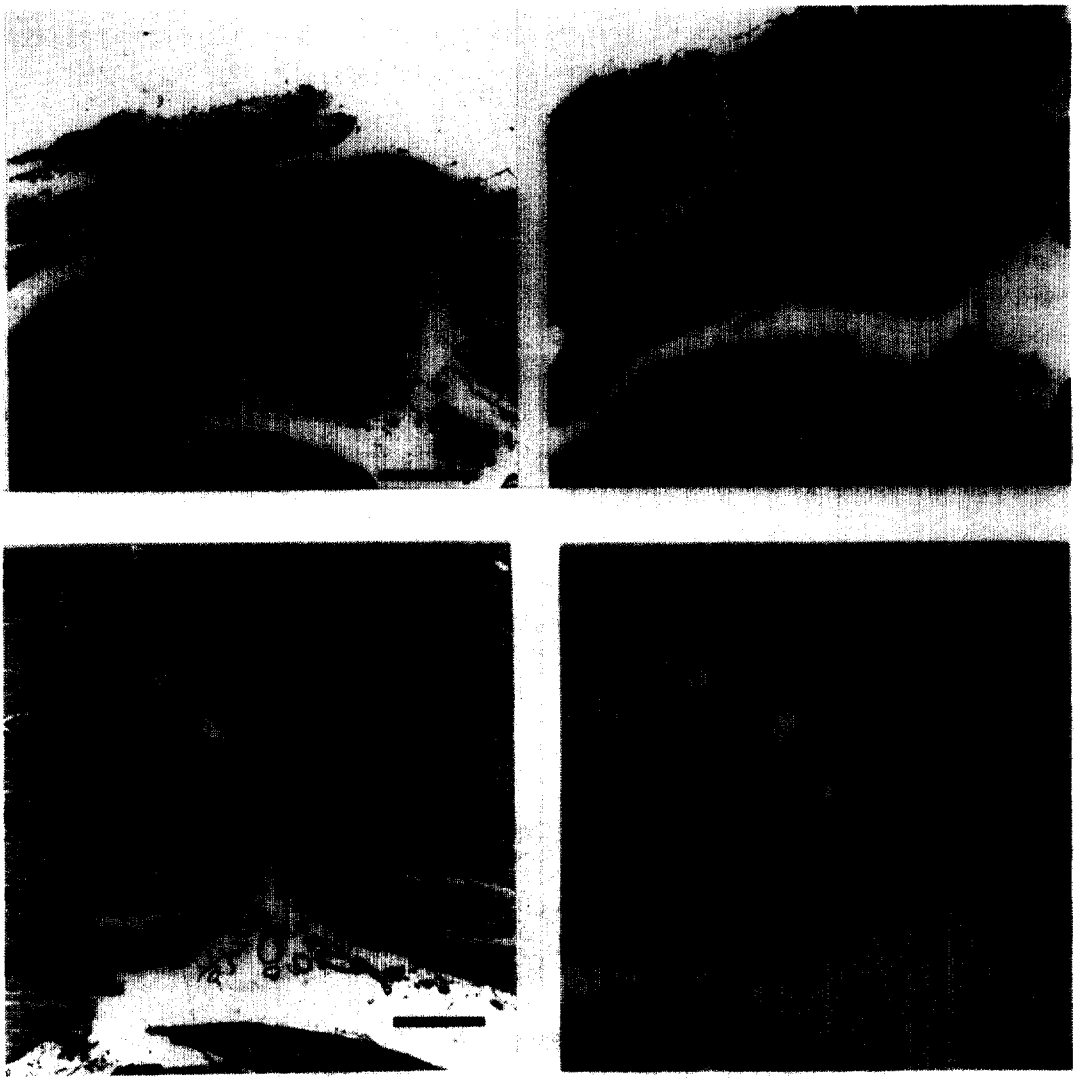

Fig.2 Coronal sections at the level 3900 μm posterior from bregma showing an overall view of the lesioned structures. The primary lesion (PL) involves all cortical laminae. Beneath of it, the hippocampal CA1 - region(CA1) and the subicular(SUB) area show neuronal scarcity. The left sections (a and c) are from the experimental animal. The sections on the right are from a sham - operated animal. Scale bars are 500 μm (a and b) and 250 μm (c and d).

tion. But the subicular part which lies next to the basal surface of the brain demonstrated a depletion of neurons(Fig, 2c) compared to control animals.

4. Lateral thalamus

Here, in one animal we found focal tissue softening. These spots contained clots of reactive glia associated with nerve cells under - going lysis (so

called " glia - nods")(Fig. 3).

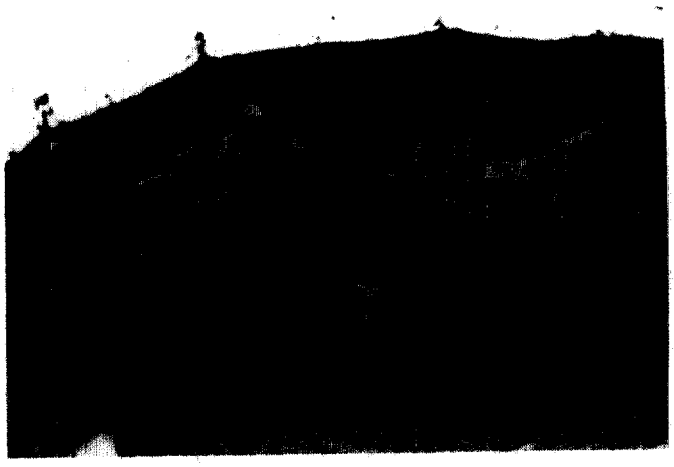

Fig.3 Experimental animal, coronal section at level 4200 μm posterior from bregma showing four lesion foci(arrows) in the lateral thalamus. Scale bar is 100 μm.

5. corpus callosum

In this structure the gliotic alteration was found bilaterally but was slightly more prominent ipsilateral to the application site. Ipsilaterally to the lesion site the hippocampal areas CA2 and CA3 seemed also to be affected in terms of neuronal scarcity(Fig. 4).

Fig.4 Shows parts of the medial neocortex, corpus callosum(CC), hippocampal areas (CA3 and CA2) and dentate gyrus(DENT) at level 1400 μm posterior from bregma in an experimental animal(left) and a sham operator control(right). Note the callosal glia proligeration and the subtotal dissolution of the hippocampal CA2 and CA3 areas ipsilaterally in contrast to the contralateral side. Scale bars are 250 μm (left) and 500 μm (right).

Discusson

These results are in good agreement to former studies with respect to their local and structural selectivity (Yokel, Provan, Meyer, & Campbell, 1988; Crapper & Dalton, 1973; Klatzo, Wisniewski, & Streicher 1965) who also found similar topic degeneration patterns by using the same toxin via different application modi.

Hippocampal, subicular and also thalamic areas turned out to be target structures of aluminium toxins - at least by direct application. The CA1 - region of the superior hippocampus and the region between the retrosplenial cortex and hippocampus (dorsal portion of the subiculum were mostly affecteded in their large pyramidal compounds. In contrast, regions like the dentate gyrus which consists of granular cells, did not show any pathological alteration.

Since the hippocampal formation is a complex heterogenous structure with respect to cell types, cell layers and nerve terminals and the aluminium - induced encephalopathy has not caused an overall neuronal loss but led only in distinct areas to degeneration, it can be argued that the substance has a cell - specific affinity and/ or the damaged cell populations bear a particular vulnerability to Al - ions at least when having contact via this route of administration. Consequently, the metal toxin caused selective, distal lesions.

Aluminium - induced encephalopathy as an animal model of human disease

Despite the fact that the histological processing together with the microscopic analysis we used in this study are not appropriate to reveal ultrastructural changes which can be found in post mortem analysis of Alzheimer - affected brains(e. g. neurofibrillary tangles NFT which are the hallmark of this degenerative disorder), the anatomical "predilection - sites" of these alterations in discussion were similar (Ishii, 1966).

Further lesion studies in connection with learning procedures should enable to clarify whether these anatomical findings are reflected by possible behavioral alterations known to be specifically modulated in neurodegenerative disorders of the Alzheimer - type.

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