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Expression of monoamine oxidase B activity in astrocytes of senile plaques

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Summary. Monoamine oxidase (MAO) histochemistry has been performed in brains from patients with dementia of Alzheimer type (DAT) and aged controls. Conspicuous MAO-positive cell clusters were frequently observed in the amygdala, hippocampus, and insular cortex in the brains of DAT. Double staining with glial fibrillary acidic protein immunohistochemistry revealed that the cluster-forming MAO-positive cells were astrocytes. Using Bielschowsky's method, Congo red and thioflavin S counterstaining, this astrocytic mass was shown to be associated with senile plaques. By the enzyme inhibition experiment, MAO activity in senile plaques was revealed to be of type B. The present results clearly indicate that MAO-B activity is expressed in fibrillary astrocytes in or around senile plaques, suggesting that these astrocytes metabolize exogenous amines in senile plaques.

Key words: Monoamine oxidase-B – Astrocyte – Senile plaques – Dementia of Alzheimer type

Monoamine oxidase (MAO; EC 1.4.3.4) has been classified into two forms, MAO-A and MAO-B, which differ in inhibitor specificities and substrate preferences [7, 8, 11, 12, 14, 18, 21, 24–27]. MAO-A has been mainly responsible for the deamination of serotonin, norepinephrine, and partially dopamine [7, 11, 14, 18, 21, 24, 25] and is selectively inhibited with low concentration of clorgyline [8, 11, 21, 26]. MAO-B, on the other hand, has been assumed to deaminate the exogenous amines as well as part of dopamine [6, 7, 11, 12, 21, 26, 27] and is selectively inhibited by L-deprenyl [6–8, 11, 12, 14, 18, 21, 24–26]. MAO-B has been described to increase with advancing age in the various regions of human brain, including the neocortex, hippocampus, caudate nucleus, hypothalamus, substantia nigra, thalamus and amygdala [1, 9, 10, 20, 22]. Increased MAO-B activity has also been reported in the neocortex and hippocampus of dementia of Alzheimer type (DAT) [1, 22, 23]. The increment of MAO-B activity in the brains of aged subjects and DAT cases has been attributed to the growth of the extraneuronal cells, such as glia, in the aging and DAT brain [22, 23].

We have studied extracranially perfused postmortem human brains using the MAO histochemical procedure and demonstrated firstly the expression of MAO enzyme activity in astrocytes in association with senile plaques. We also present here evidence suggesting that MAO in these astrocytes is of type B.

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Materials and methods

Four DAT cases [78-year-old (y-o) male, 75-y-o female, 83-y-o female, 88-y-o female] and four non-demented controls (68-y-o male, 72-y-o female, 80-y-o female, 82-y-o female) were studied in the present study. The DAT cases were clinically diagnosed as DAT and confirmed pathologically by the presence of diffuse cortical atrophy, abundant senile plaques and neurofibrillary tangles in the neocortex. No neurological abnormalities were found in control cases. Neuropathological examinations revealed many senile plaques in a control case (82-y-o female), although none or few in the other three controls. All cases examined here were not medicated with psychotropic drugs including antidepressants within at least a few days before death. Postmortem human brains were perfused extracranially within 7 h after death by the method by Beach et al. [3]. Briefly, brains were perfused with 1 l of ice-cold 0.01 M phosphate-buffered saline (PBS, pH 7.4) bilaterally through the vertebral and internal carotid arteries, followed by 3 l of an ice-cold fixative consisting of 0.35% glutaraldehyde and 4% paraformaldehyde in 0.1 M phosphate buffer (PB). The brains were cut coronally into 1- to 2-cm-thick blocks. Tissue blocks, including either the insular cortex, caudate nucleus, putamen, globus pallidus, hypothalamus, thalamus, hippocampus, amygdala, substantia nigra, or dorsal raphe, were dissected out. Tissue blocks from three brains (one DAT and two controls) were fixed with a post-fixative consisting of 4% paraformaldehyde in 0.1 M PB for 24–48 h at 4°C, tissue blocks from another brain (a control) were immersed in the post-fixative for 1 h at 4°C, and soaked in the cryoprotectant containing 15% sucrose in 0.1 M PB for 24 h at 4°C. Tissue blocks from four brains (three DAT cases and a control) were placed immediately after

perfusion in the cryoprotectant for 24 h at 4° C. Fifty- to eighty-μm-thick sections were cut on a freezing microtome and stored in 0.05 M Tris-HCl-buffered saline (pH 7.6) at 4°C until use for the histochemical procedure, in which condition the histochemical enzymatic activity was preserved up to at least 3 months.

The MAO enzyme histochemistry was performed according to the method by Kishimoto et al. [16] and Arai et al. [2]. Sections were treated in the free-floating condition throughout the procedure of both MAO histochemistry and glial fibrillary acidic protein (GFAP) immunohistochemistry. Sections were thoroughly washed with 0.05 M Tris-HCl buffer (TB, pH 7.6) and immersed in a reaction medium for 24–48 h at 4°C. The medium consisted of 75 mg tyramine hydrochloride (Nacalai Tesque Inc, Japan) 5 mg diaminobenzidine tetrahydrochloride (DAB, Dojin Co, Japan), 100 mg horseradish peroxidase (Toyobo Co, Grade III, Japan), 600 mg nickel ammonium sulfate (Nacalai Tesque Inc), and 65 mg sodium azide (Nacalai Tesque Inc) in 100 ml of 0.05 M TB (pH 7.6). The reaction was stopped by replacing the sections in TB. To examine the relationship between MAO activity and astrocytes, GFAP immunohistochemistry was performed as follows; MAO-stained sections were washed with 0.1 M PBS and incubated in 0.3% H_2O_2 in 0.1 M PBS for 30 min at room temperature to block endogenous peroxidase, and incubated in anti-bovine GFAP serum (Dako, Denmark) diluted (1:4000) in 0.1 M PBS containing 0.3% Triton X-100 (PBST) for 24 h at 4°C. After washing with PBST, sections were immersed in biotinylated anti-rabbit IgG (Vector Labs, USA) diluted in PBST (1:200) for 1 h at room temperature and then, after washing, placed in avidin-biotin peroxidase compex (Vector Labs) diluted in PBST (1:200) for 1 h at room temperature. After rinsing with 0.05 M TB (pH 7.6), sections were incubated in 0.05 M TB (pH 7.6) containing 0.02% DAB and 0.005% H_2O_2. In the present double-staining method of GFAP and MAO, MAO activity was shown as dark-blue reaction precipitates and GFAP as light brown [17, 28]. Some of the MAO-stained sections from all cases examined in the present study were fixed with 4% paraformaldehyde in 0.1 M PB for 6 h at room temperature, mounted on gelatin-coated glass slides and counterstained with either thioflavin S (Sigma Co, USA), Bielschowsky silver impregnation method, or Congo red (Nacalai Tesque Inc). The mounted sections were air dried, washed with tapping water, dehydrated with graded alcohol, cleared by xylene and coverslipped with Entellan new (Merck, FRG).

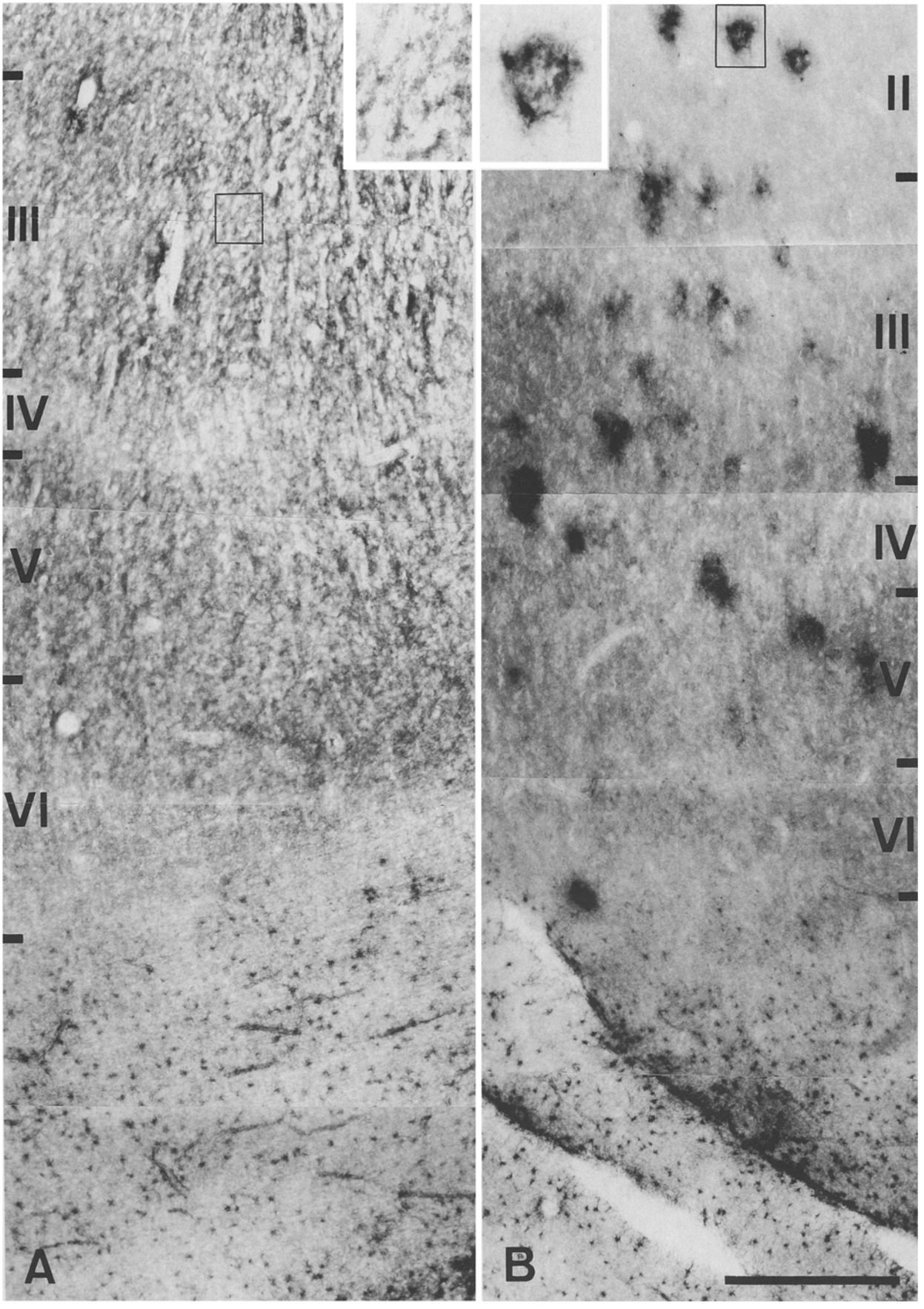
As a histochemical control experiment, sections from the normal controls and DAT cases were incubated in the reaction medium with the omission of tyramine hydrochloride. The enzyme inhibition experiment was performed as follows. Sections were incubated in 0.1 M PBS containing 10^{-3} to 10^{-10} M L- deprenyl (Research Biochemicals Inc, USA) or 10^{-4} to 10^{-10} M clorgyline hydrochloride (Research Biochemicals Inc) for 1 h at room temperature. Sections were thoroughly washed with 0.1 M PBS and then 0.05 M TB for at least 1 h at room temperature, and staining for MAO histochemistry in the same way as described above. Since the post-fixation apparently reduced the staining intensity as described below, the inhibition experiment was done in sections from tissue blocks without the post-fixation.

Results

The most intense staining was observed in sections both without post-fixation and with 1-h post-fixation. In case of 1-h post-fixation, however, a superficial area of 1–2 mm width of the sections showed no histochemical reaction, which seemed to have been caused by the destruction of the enzyme activity by the post-fixative. A positive reaction was also observed in sections from blocks of 24- to 48-h post-fixative, although only in the sections from the deep part of tissue blocks. In this case, it was assumed that the enzymatic activity of the deep part of the tissue blocks was not fully affected by the immersion in the post-fixative for up to 48 h.

A positive reaction was observed in neurons and glial cells in sections of both the control and DAT cases. The positive neurons were observed in some subcortical nuclei, which will be described elsewhere. In the neocortex of any cases examined here, no MAO-positive neuronal somata was observed. However, many glial cells were stained in the subcortical white matter (Fig. 1). The glial staining in the subcortical white matter appeared somewhat more intense around the vessels. As shown in Fig. 1, the MAO glial staining in the subcortical white matter appeared similar among the control and DAT cases. The characteristic finding in brains from four DAT cases and a non-demented case (82-y-o female) with Alzheimer's pathology [15] was the presence of round- or oval-shaped MAO-positive mass (Fig. 1B). These masses were 50–200 μm in diameter, which appeared to consist of two to ten cells positive for MAO histochemistry. These cells were small or medium in size (10–15 μm × 10–15 μm) and showed some ramified processes (Figs. 2, 3). The cell clusters were observed in the insular cortex, amygdala, hippocampus, putamen and dorsal raphe, although the numerical density of cell clusters were clearly different among the brain regions examined. These clusters were most frequently observed in the amygdala, hippocampus and insular cortex. As shown in Fig. 1A, no MAO-positive mass was observed in controls except for a control case with Alzheimer's pathology. Careful examination of GFAP-immunohistochemically counterstained sections showed that MAO-positive cells were also stained immunoreactive for GFAP (Fig. 2A). As seen in this figure, astrocytes negative for MAO were also observed. The double staining with Bielschowsky's method revealed that astrocytic clusters were in or around senile plaques (Fig. 2B). On the other hand, in control cases in which senile plaques were absent, the present double-labelling procedure with MAO and Bielshowsky's method stained no plaque-like structures. Observation of sections counterstained with Congo red under polarized light showed the frequent presence of amyloid core deposits around the central part of the clusters (Fig. 2C, D). This finding

Fig. 1A, B. Photomontages of monoamine oxidase (MAO)-stained sections in the insular cortex of a non-demented control case [72-year-old (y-o) female] (**A**) and a case with dementia of Alzheimer type (DAT; 75-y-o female) (**B**). In **A**, MAO-positive reaction is observed in the cortical gray and subcortical white matter. In this cortical gray matter, diffuse background staining is observed. The *inset* shows a higher-power view of the area indicated with a *rectangle*, in which many fusiform-shaped areas, possibly representing neuronal or glial somata, are devoid of staining. Many MAO-positive cells are scattered in the subcortical white matter. These small cells in the subcortical white matter appear to be astrocytes on the basis of their morphologies and cell sizes. In **B**, abundant MAO-positive masses are observed in the gray matter, while the histochemical feature of the subcortical white matter appears similar to that in **A**. As shown in the *inset* at a higher magnification of the area shown with a *rectangle* in **B**, the mass appears to consist of some small cells and their processes. Scale bar = 500 μm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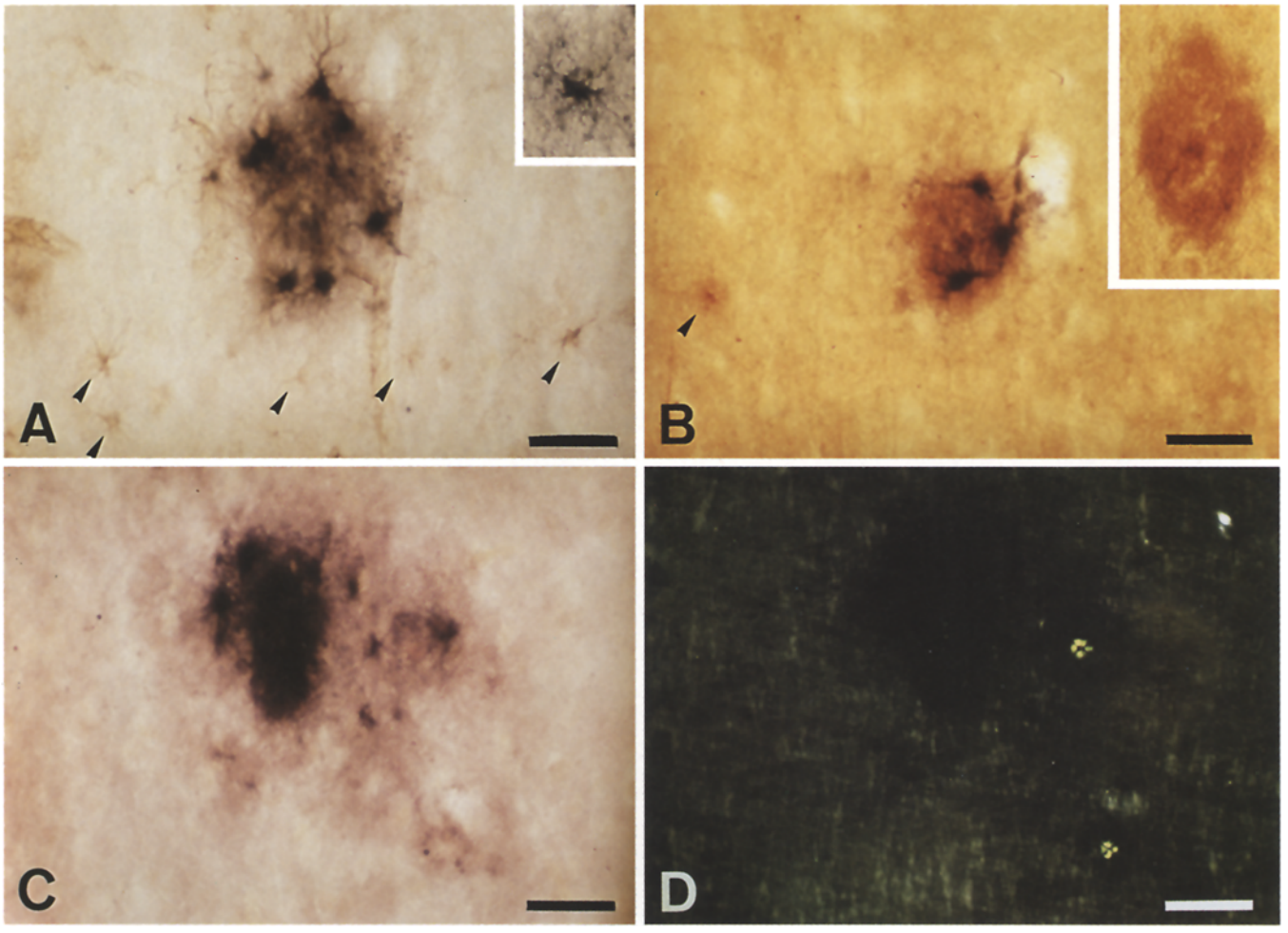

Fig. 2A–D. Double staining for MAO and glial fibrillary acidic protein (GFAP) immunohistochemistry (**A**) in a case with DAT (75-y-o female). Processes of MAO-positive (blue-black) astrocytes are stained immunoreactive for GFAP (brown). *Arrowheads* indicate MAO-negative and GFAP-immunopositive astrocytes. The *inset* shows an example of an MAO-positive astrocyte which was not processed for GFAP immunohistochemistry, in which the positive reaction appears dark-blue. Double staining for MAO and Bielschowsky's method in DAT case (75-y-o female) demonstrates that astrocytic clusters are in association with senile plaques (**B**). The *inset* shows an MAO-negative senile plaque of the similar size. The *arrowhead* indicates a small plaque negative for MAO histochemistry. Double staining for MAO and Congo red in a DAT case (75-y-o female) (**C** and **D**). Under polarized light (**D**), amyloid deposits colored apple-green are observed. **A–D** Scale bar = 50 μm

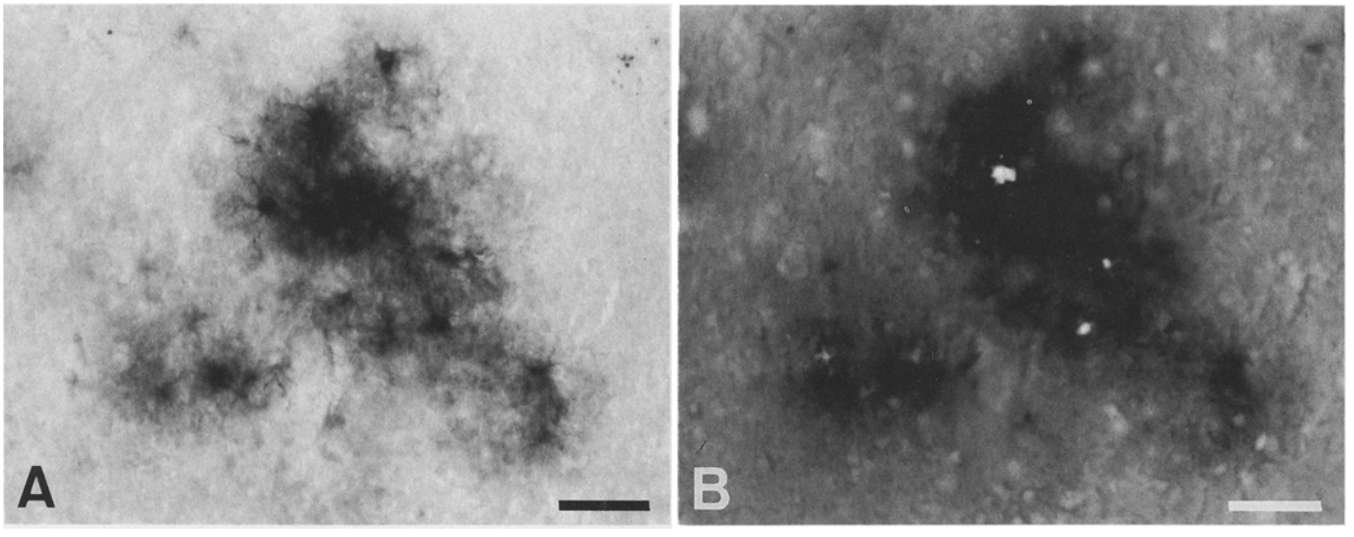

Fig. 3A, B. Double staining for MAO and thioflavine S in a DAT case (75-y-o female). Under the epifluorescence microscopy, amyloid cores stained with thioflavin S (**B**) are observed near around the central part of the MAO-positive mass (**A**). Scale bar = 50 μm

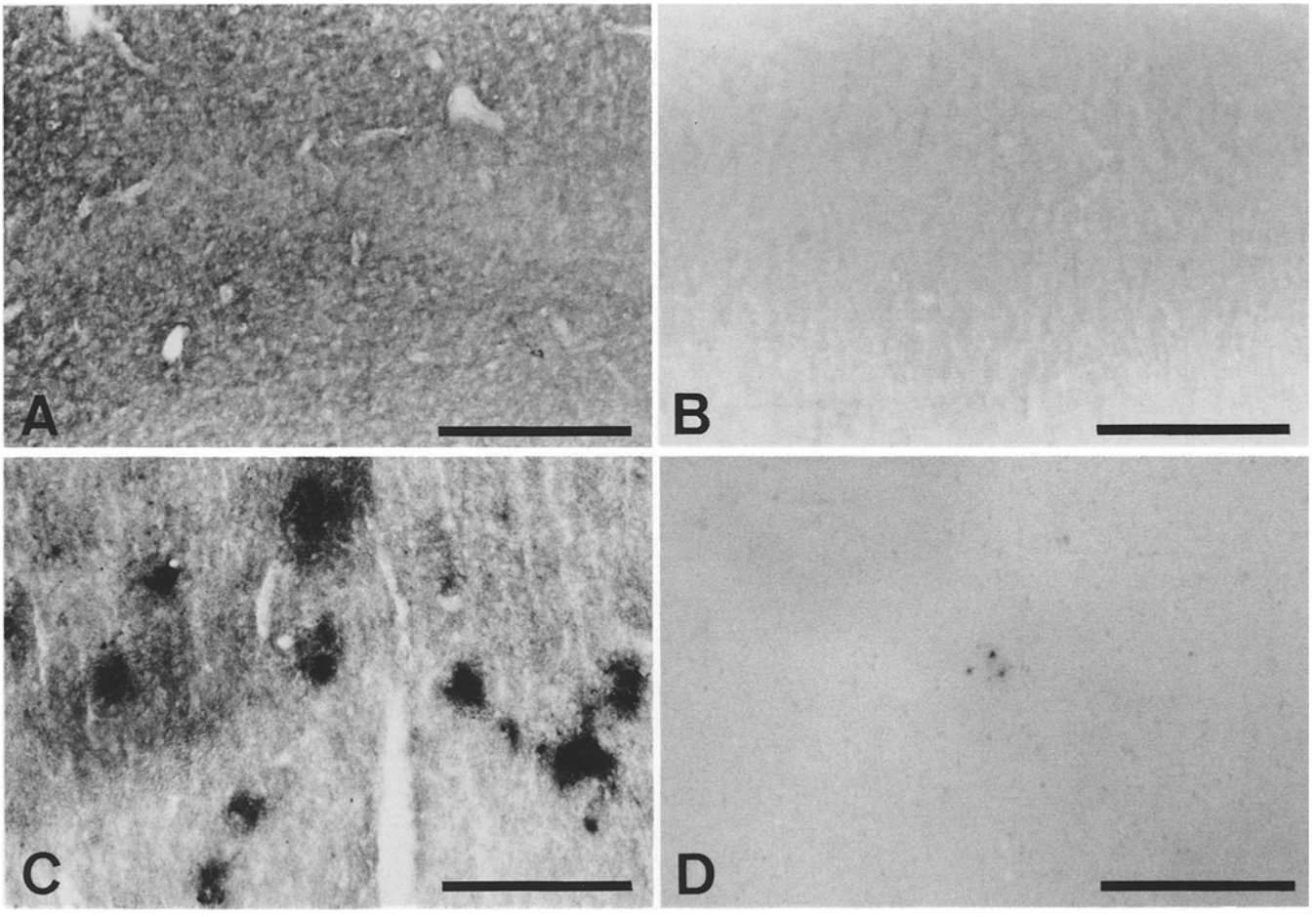

Fig. 4A – D. Specificity tests of the present MAO histochemistry. In a control case (72-y-o female), diffuse background staining for MAO is observed in the insular cortex (**A**). **B** demonstrates a neighboring section of **A** stained for MAO after pretreatment with 10^{-5} M L-deprenyl, in which no MAO staining is observed. **C** shows the insular cortex of a DAT case (75-y-o female) stained without the inhibitor pretreatment, in which abundant MAO-positive masses are observed. L-Deprenyl (10^{-5} M) pretreatment extremely reduced MAO staining in a neighboring section of **C** and faintly stained astrocytic clusters are rarely observed (**D**). Scale bar = 500 μm

was confirmed by observation of sections counterstained with thioflavin S under epifluorescence microscopy (Fig. 3A, B). Most of the astrocytic clusters positive for MAO histochemistry were observed in association with senile plaques. This was not the case for senile plaques versus MAO-positive astrocytic clusters. As shown in Fig. 2B, senile plaques without astrocytic MAO activity were occasionally found. Approximately 70% to 90% of senile plaques showed MAO activity.

In MAO histochemical control sections, in which the histochemical reaction was done in an identical staining medium except for omission of the substrate, no reaction product was observed in any sections from both the normal controls and DAT cases. Astrocytic MAO staining in the senile plaque was almost completely inhibited by pretreatment with L-deprenyl at a concentration higher than 10^{-5} M (Fig. 4). At this concentration, the astrocytic staining in the subcortical white matter was completely abolished. Pretreatment with 10^{-6} M L-deprenyl extremely reduced astrocytic MAO staining, and faint staining was observed in some senile plaques and a limited number of astrocytes surrounding the blood vessels. Although 10^{-7} M L-deprenyl partially inhibited glial MAO staining, no effect was observed with 10^{-8} to 10^{-10} M. Preincubation with clorglycine hydrochloride at concentrations lower than 10^{-5} M did not affect MAO activity in the senile plaque, although partial inhibition was observed by pretreatment with clorgyline hydrochloride at 10^{-4} M.

Discussion

In experiments in vitro, 90% – 100% inhibition of type B MAO has been observed with preincubation by L-deprenyl at concentrations of 10^{-4} M in the human cortex [11], 10^{-4} M [14] and 10^{-6} M [7] in the rat liver. In the present study, glial MAO activity was almost completely inhibited with L-deprenyl at equal or lower concentrations. Since, in addition, high concentration of chlorgyline hydrochloride, such as 10^{-4} M, also inhibits MAO-B activity [7, 8, 11, 12, 18], partial MAO inhibition with 10^{-4} M clorgyline hydrochloride in the present study might be caused by MAO-B inhibition by clorgyline

hydrochloride. Double staining with GFAP immunohistochemistry and MAO histochemistry has revealed that the MAO-positive mass in DAT brain consisted of astrocytes. Thus, the present results clearly indicate that the histochemical reaction in glial cells in the present study represents MAO enzyme activity and that fibrillary astrocytes in association with senile plaques contain type B.

The recent immunohistochemical study demonstrated that glial cells in the non-human primates and human brain exhibited MAO-like immunoreactivity of both types, A and B [19, 29, 30]. In addition, glia from the human frontal cortex has been described to contain both types of MAO activity [26]. However, in the present study MAO-A activity was not detected in the astrocytes. Although the reason for this discrepancy between our results and others has yet to be determined, two possible causes could be pointed out; (1) some technical problem, including fixation and agonal conditions of cases examined in the present study, destroyed MAO-A activity in the astrocyte; and (2) glial MAO-A activity in the postmortem human brain is under the detectable range of the present method which is based on the MAO enzymatic reaction. MAO-A enzymatic activity might be more affected with aldehyde fixative or agonal condition than MAO-B, although no data on this has so far been reported. Riederer et al. [26] have shown that the ratio of MAO-B enzymatic activity versus MAO-A activity was 7.5:1 in glial cells in the human frontal cortex. The recent immunohistochemical study also showed that MAO-B immunostaining was much more consistent than MAO-A staining in the glial cell of the human brain [30]. In contrast, the other immunohistochemical study using the different antibody demonstrated that the glial cells displayed both MAO-A and MAO-B immunoreactivities of almost identical intensity in the normal human brains [19]. It may be possible that some differences in the immunohistochemical results in the different laboratories arise from the different antibodies recognizing different epitopes of the protein, which could cause some qualitative or quantitative variance in the immunohistochemical staining. Thus, to clarify this further studies will be necessary using the multiple techniques.

In vitro studies have demonstrated the increased activity of MAO-B without accompaying MAO-A change in Alzheimer's disease (AD) brain [1, 22, 23]. It has been assumed that increased MAO-B activity in AD brain results from the glial outgrowth [22, 23]. The present study indicates that reported MAO-B increment in various regions of AD brain is at least partly due to the occurrence of MAO-B activity of astrocytes in senile plaques.

The pathophysiological role of MAO-B activity in astrocytes in senile plaques are yet to be determined. Although dopamine has been reported to be a substrate for MAO-B in the human brain [12, 25], it seems unlikely that astrocytes in or around senile plaques exhibit MAO-B activity to metabolize dopamine, since the contents of dopamine and its metabolites have been described to be unchanged or even slightly decreased in AD cortex compared with controls [5, 23, 31]. It has been shown that MAO-B oxidatively deaminates the exogenous amines [6], including neurotoxins such as the parkinsonism-inducing tertiary amine, MPTP [4, 13]. Although no toxic amines have been identified in senile plaques, MAO-B expressed in senile plaques might be involved in metabolizing extraneous amines within senile plaques. Further studies are needed to address this assumption.

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