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Brain gamma-aminobutyrate aminotransferase (GABA-T) and monoamine oxidase (MAO) in patients with Alzheimer's disease

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Summary. Activities of Gamma-aminobutyrate aminotransferase (GABA-T) and Monoamine oxidase (MAO)-A and -B were estimated in postmortem brains from 6 control subjects without psychiatric or neurologic disorders and 8 histopathologically verified cases of patients with Alzheimer's disease and senile dementia of Alzheimer type (AD/SDAT). The enzyme activities were examined in four cortical brain regions, three nuclei in the basal ganglia, thalamus and white matter. GABA-T activities in the cortical regions (frontal, parietal, occipital and temporal cortices) and nucleus caudatus were significantly lowered in the AD/SDAT patients. The MAO-A activities were significantly increased in the occipital cortex, caudate nucleus, thalamus and white matter in the AD/SDAT patients. No significant differences were found in the other regions (frontal cortex, parietal cortex, temporal cortex, putamen and globus pallidus). The MAO-B activities in three cortical regions (frontal, parietal and occipital cortices), thalamus and white matter were significantly increased in the AD/SDAT patients, whereas no difference was apparent in the other regions. The changed activities could not be correlated with age or postmortem time. The present results are the first describing decreased GABA-T activities as well as increased MAO-A activities in brain from patients with AD/SDAT, while the results with MAO-B support previous findings. A possible connection was found between the order of magnitude of the changes in enzyme activities and the severity of the disease.

Keywords: Aminobutyrate aminotransferase, Alzheimer's disease, monoamine oxidase, human brain, postmortem brain.

Introduction

Alzheimer's disease and senile dementia of Alzheimer type (AD/SDAT) are neurodegenerative disorders characterised clinically by dementia, anatomically

by cortical and white matter atrophy and histologically by the presence of neurofibrillary tangles and neuritic (senile) plaques (see Tomlinson et al., 1970; Roth, 1986). Neurochemical studies in AD/SDAT brains indicate deficiencies in several transmitter systems, including both the monoaminergic and the GABAergic systems (Gottfries, 1985; Hardy et al., 1985; Ellison et al., 1986; for a review see Gottfries, 1990).

Human brain monoamine oxidase (MAO; E.C.1.4.3.4) activitiy can be divided into two forms: MAO-A which is mainly responsible for the oxidative deamination of 5-hydroxytryptamine (5-HT), noradrenaline (NA) and partially dopamine (DA); and MAO-B which catalyzes the oxidative deamination of several exogenous amines, as well as part of DA (Fowler, 1982). It has, since a long time, been known that in the human brain, MAO-B activity, in contrast to MAO-A, increases with age (Fowler et al., 1980). The increase in MAO-B activity seems to be rather uniform throughout the brain, with the exception of the lower parts, such as brain stem and medulla oblongata, where the rate of increase is lower (Fowler et al., 1980). A further increase in MAO-B activity than expected from age has been found in brains from patients with Alzheimer's disease (Adolfsson et al., 1980; Oreland and Gottfries, 1986; Reinikainen et al., 1988; Jossan et al., 1991), and, as was the case in normal aging (Fowler et al., 1980), the increase was due to an increased V_{max}, rather than a change in K_m (Oreland and Gottfries, 1986). Furthermore, the increase in MAO-B activity was highly correlated to the binding of deprenyl using an autoradiographical technique, which again indicates that the increase is due to an increased concentration of otherwise unchanged MAO-B molecules (Jossan et al., 1991). The simplest explanation for these phenomena is based on results obtained after mechanical or biochemical lesions of rat brains. When rats were transected on one side of the brain with a loss of nerve terminals distal of the section as a result, MAO-B but not MAO-A activity was increased, while no changes in MAO-B activities occurred on the unoperated side (Oreland et al., 1980). The increase in MAO-B activity, both after hemistransection and with age, has been shown to be entirely due to an increase in the extraneuronal component of the enzyme (Stenström et al., 1985; Arai et al., 1985). Similar results have been obtained with neurotoxins of various kinds (Schoepp and Azzaro, 1983; Francis et al., 1985; Melamed et al., 1985; Jossan et al., 1989). Thus, some form of reactive proliferation of glial cells, rich in MAO-B, is consistent with the observed increase in MAO-B activity (Demarest et al., 1980; Oreland et al., 1980, 1983; Riederer and Jellinger, 1983). The notion that the increase in MAO-B activity in neurodegenerative disorders is linked to gliosis involving astrocytes, was recently strongly supported by the findings of an expression of MAO-B activity in astrocytes of senile plaques (Nakamura et al., 1990).

Gamma-aminobutyrate aminotransferase (GABA-T; E.C.2.6.1.19) is an enzyme that inactivates the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). It has been postulated that alterations in GABA neurotransmission might play a role in the pathophysiology of a number of disorders such

as Huntington's disease, tardive dyskinesia, epilepsy, Parkinson's disease, anxiety and depressive illness (Enna et al., 1977; Teychenné et al., 1982; Van Kammen et al., 1982; Lloyd et al., 1985). Also with regard to Alzheimer's disease (AD), it has been suggested that there is a disturbance in the GABAergic system, since low levels of GABA have been reported both in the cerebrospinal fluid (CSF) (Enna et al., 1977; Bareggi et al., 1982; Zimmer et al., 1984) and in postmortem brains from such patients. The findings about brain levels of GABA, however, are contradictory. Thus, Rossor et al. (1982), in an initial study on brain tissue from elderly patients with SDAT, found only minor changes in GABA levels, but subsequently reported that younger patients with AD (aged less than 79 years) had a 30 to 40% reduction, both frontal and temporal cortices (Rossor et al., 1984). Arai et al. (1985 a) also reported about reduced GABA levels in the inferior temporal cortex in patients with AD, which could not, however, be confirmed in a subsequent study (Sasaki et al., 1986). Ellison et al. (1986) found significant reductions in GABA concentrations in all regions examined in AD cerebral cortex, which is consistent with the report of Hardy et al. (1987). Beal et al. (1989, 1990), on the other hand, found no change in cortical GABA concentrations in brains from patients with AD/SDAT.

The study of GABAergic systems in postmortem samples is complicated when using biochemical markers. Thus, concentrations of GABA increases after death (Rossor and Iversen, 1986) and the synthesising enzyme of GABA, glutamic acid decarboxylase (GAD), is known to be sensitive to premortem conditions, particularly to anoxia, reduced blood flow and prolonged illness with coma (Bowen et al., 1977; Perry et al., 1978; Monfort et al., 1985). With regard to brain GABA-T, however, we recently carried out a detailed study on the effect of premortem conditions on a series of suicide cases and controls. In this study only death by carbon monoxide poisoning seemed to affect the GABA-T activity in the frontal cortex (Sherif et al., 1991 a). To our knowledge, brain GABA-T activity, has never been studied in AD/SDAT.

In the present study the possible use of brain GABA-T activity as a biochemical marker for AD/SDAT has been investigated. In addition, for further exploration of the changes of MAO-A and − B in such brains, those enzyme activities were estimated.

Materials and methods

Materials

This study includes brains from six matched (see below) control subjects and from eight patients with AD/SDAT. No subject in the control group had any known history of psychiatric or neurological disorder.

The AD/SDAT group includes patients with clinically diagnosed dementia. Dementia was established according to the DSM-III criteria (American Psychiatric Association, 1987). The known history of dementia varies between 2–14 years. The NINCDS-ADRDA criteria for probable AD (Mckhann et al., 1984) were applied and included the presence of progressive dementia with deficits in two or more regions of cognition. One of the patients had, however, an onset of the dementia at the age of 93 years. One patient with a typical

clinical picture had concomitant symptoms of Parkinsonism. However, at the autopsy there was in this case a normal pigmentation of the substantia nigra. Two of the patients were diagnosed as Alzheimer's disease type I (pure AD with early onset) while 6 were diagnosed as type II (less focal symptomatology and late onset) (Blennow, 1990). Six patients were rated according to a rating scale constructed for posthumous rating (Adolfsson et al., 1981). All the rated patients were according to the ratings severaly demented (Score 54, 57, 49, 54, 51, 58, ?, ? score variance: 0–58 with 0 indicating no intellectual impairment).

The clinical diagnoses were confirmed at the macroscopic postmortem inspection of the brain. None of the brains had severe arteriosclerosis of the brain vessels, encephalomalacias or other findings that could explain the dementia disorders. In 6 of the 8 cases the diagnosis was confirmed by histopathological investigation. In 2 cases the histopathology is missing, but as the postmortem microscopic investigation of these brains excluded disorders as vascular dementias and the clinical picture supported the AD/SDAT diagnosis, they were included. The case with an onset of dementia at 93 years had tangles in the cortical regions and in great amounts in the hippocampus. Plaques were found in cortical regions and in hippocampus in increased amounts, but neurons were rather well preserved.

The cases were sex- (controls: 3 F and 3 M; AD/SDAT: 4 F and 4 M) and age-matched (controls: 74.8 ± 7.2 years; AD/SDAT: 82.0 ± 3.5 years). Postmortem time was 86.0 ± 18.3 hours for the control subjects and 61.9 ± 13.2 hours for the AD/SDAT patients. Animal and human studies on the postmortem stability have indicated the stability of GABA-T and MAO activities up to 120 hours (Fowler et al., 1980; Sherif et al., 1991). It has also previously been shown that freezing before dissection of tissues does not affect the MAO and GABA-T activities (Gottfries et al., 1975; Fowler et al., 1980; Sherif et al., 1991). Neither does storage at − 80 °C affect the MAO or GABA-T activities (Mackay et al., 1978; Sherif et al., 1991). Details of the controls and patients are given in Table 1. Moreover, death occurred relatively quickly in all the cases, generally after a period normal or near normal health (group A according to the classification of agonal status by Perry et al., 1982).

Biochemical methods

GABA-T assay

The brain tissue was homogenised by 6 strokes at 600 rpm in 20 volumes of buffer (0.1 M disodium phosphate, 0.1 mM EDTA, 0.5 mM dithiothreitol and 0.2 mM pyridoxal phos-

Table 1. General features of AD/SDAT patients and control subjects

Data	Control subjects	AD/SDAT patients
n	6	8
Sex	3 F, 3 M	4 F, 4 M
Age, yr	74.8 ± 7.2	82.0 ± 3.5
(range)	(53–98)	(65–98)
Postmortem time, h	86.0 ± 18.3	61.9 ± 13.2
(range)	(46–168)	(28–142)

Values as mean ± SEM, range is given in brackets.

There were no statistically significant differences between the groups (unpaired *t*-test)

phate, pH 8.4) in a Potter-Elvehjem glass/Teflon system. GABA-T activity was estimated by measuring the formation of (^{14}C)-succinic semialdehyde under standard conditions. Further details are given in Sherif et al. (1991). Briefly, standard assays contained the following components in a final volume of 100 µl: 25 µl of incubation medium (0.05 mM EDTA, 0.25 mM dithiothreitol, 0.1 mM pyridoxal phosphate and 50 mM disodium phosphate; pH 8.4), 25 µl of 0.68 mM alpha-ketoglutarate and 25 µl of tissue homogenate in the buffer. The substrate (25 µl at a concentration of 2 mM; ^{14}C-GABA) (NEN Research Products, Boston, Mass) was added and the sample incubated at 37 °C for 30 min. The reaction was terminated on ice and by addition of 30 µl of 1 M HCI to the reaction mixture. Blanks were prepared by substitution of alpha-ketoglutarate for disodium phosphate (0.05 M; pH 8.4). The incubates were passed through an ion-exchange columns (Bio-Red Laboratories AG 50W-X8 resin) into scintillation vial. Scintillation liquid (15 ml; Ready Protein ^{TM}) was added and radioactivity counted in a liquid scintillation counter. All assays were performed in triplicate. The reproducibility of the assay was tested by estimating a sample from a normal control cortex several times. The intra-assay coefficients of variation of the assay for GABA-T was found to be less than 6%, (0.923 ± 0.037, mean ± S.D., n = 7).

MAO assay

MAO-A and -B activities were assayed in the homogenates by a conventional radiochemical method (Eckert et al., 1980) with ^{14}C-5-hydroxytryptamine (5-HT) and ^{14}C-2-phenylethylamine hydrochloride (PEA) (NEN Research Products, Boston, Mass) respectively, as substrates. Briefly, brain tissue was homogenised by 6 strokes at 600 rpm in 9 volumes of ice cold sucrose (0.32 M) in a Teflon/glass motorised tissue grinder. The homogenates were diluted with 9 volumes of 10 mM Na-K phosphate buffer, pH 7.4. Fortly µl of the homogenate was then incubated for 20 min at 37 °C with 0.1 mM 5-HT and for 5 min at 37 °C with 0.05 mM PEA as substrates, respectively, in a total volume of 100 µl. Incubation was terminated by acidification with 20 µl of 3 M HCI and the acid metabolites formed extracted into 1 ml toluene: ethyleacetate 1 : 1, saturated with water. Radioactivity was estimated by liquid scintillation counting using scintillation fluid (8 ml; Ready Safe^{TM}). All assays were performed in triplicate. The intra-assay coefficients of variation of the assay for MAO was found to be less than 5%, (MAO-A was 0.177 ± 0.006 and for MAO-B was 0.864 ± 0.028, mean ± S.D., n = 7).

Protein assay

The protein concentrations of brain homogenates were estimated by the method of Lowry et al. (1951) as modified by Markwell et al. (1978) with bovine plasma albumin as a standard.

Results

The main characteristics of the AD/SDAT patients and the control subjects with regard to age, postmortem time (the time between death and storage of the tissue at − 80 °C) and sex are shown in Table 1. There were no significant differences between AD/SDAT patients and the control subjects.

Brain GABA-T

Table 2 shows GABA-T activities in various regions of postmortem brains of control subjects and AD/SDAT patients. There was a significant reduction in GABA-T activities in the AD/SDAT patients in all cortical regions investigated

Table 2. Activity of GABA-T in AD/SDAT brain regions compared to control subjects

Brain region	Control subjects	Alzheimer patients	Mean % of controls
Cortical regions			
Frontal C.	0.952 ± 0.072	0.707 ± 0.052***	74
Parietal C.	0.999 ± 0.057	0.713 ± 0.064***	71
Occipital C.	0.946 ± 0.062	0.773 ± 0.054*	82
Temporal C.	0.979 ± 0.097	0.753 ± 0.071*	77
Basal ganglia			
Caudate nucleus	1.326 ± 0.071	1.121 ± 0.044**	85
Globus pallidus	0.859 ± 0.096	0.852 ± 0.042	99
Putamen	0.988 ± 0.082	0.960 ± 0.112	97
Thalamus	0.956 ± 0.105	0.831 ± 0.056	87
White matter	0.233 ± 0.025	0.247 ± 0.017	106

Values (nmole per min per mg protein) are expressed as means ± SEM.
Significantly different from controls by unpaired *t*-test (* $p < 0.05$; ** $p < 0.025$; *** $p < 0.01$)

as well as in the caudate nucleus. In the basal ganglia, however, the activity in the globus pallidus and putamen were unchanged. In the thalamus, there was no statistically significant difference, but the mean value was of the same order as that of caudate nucleus, i.e. appr. 85% of the controls. The GABA-T activity in the white matter did not differ between the two groups.

Brain MAO

When brain MAO activities in the AD/SDAT patients were compared with the control subjects, the MAO-A activity was found to be significantly increased (34% of control value, $p < 0.05$) in the occipital cortex (Table 3). No difference was found in the other cortical regions. In the basal ganglia, there was a significant increase in the caudate nucleus with no change in the globus pallidus and putamen. With regard to the latter region, however, the mean activity was increased with appr. 50% but with a considerable variation. In the thalamus, the MAO-A activity was significantly increased (appr. 40%, $p < 0.025$) and in the white matter the MAO-A activity was increased 2½ fold (Table 3).

With respect to MAO-B activity, an increased activity was found in the brains of the AD/SDAT patients in all cortical regions (45–94%), however, not reaching statistical significance in the temporal part (Table 4). In the basal ganglia, no statistically significant difference was found, although the mean of the activity of the AD/SDAT patients in the putamen was 157% of that of the controls. In the thalamus there was a significant increase of about 50% in the AD/SDAT patients and in the white matter their MAO-B activity was almost two-fold that of the controls (Table 4).

Table 3. Activity of MAO-A in brain regions of patients with AD/SDAT

Brain region	Control subjects	Alzheimer patients	Mean % of controls
Cortical regions			
Frontal C.	0.178 ± 0.014	0.204 ± 0.032	115
Parietal C.	0.169 ± 0.015	0.217 ± 0.035	128
Occipital C.	0.175 ± 0.015	0.234 ± 0.027*	134
Temporal C.	0.175 ± 0.005	0.160 ± 0.009	92
Basal ganglia			
Caudate nucleus	0.168 ± 0.005	0.217 ± 0.021*	129
Globus pallidus	0.166 ± 0.031	0.181 ± 0.013	109
Putamen	0.140 ± 0.014	0.204 ± 0.030	146
Thalamus	0.208 ± 0.021	0.288 ± 0.022**	139
White matter	0.058 ± 0.006	0.148 ± 0.030**	255

Activity of MAO-A is given as mean ± SEM in nmole per min per mg protein.
* $p < 0.05$; ** $p < 0.025$, *t*-test (unpaired)

Table 4. Activity of MAO-B in brain regions of patients with AD/SDAT

Brain region	Control subjects	Alzheimer patients	Mean % of controls
Cortical regions			
Frontal C.	0.860 ± 0.093	1.326 ± 0.190*	154
Parietal C.	0.697 ± 0.089	1.351 ± 0.206**	194
Occipital C.	0.678 ± 0.146	1.122 ± 0.166*	166
Temporal C.	0.724 ± 0.105	1.048 ± 0.191	145
Basal ganglia			
Caudate nucleus	1.651 ± 0.117	1.785 ± 0.186	108
Globus pallidus	1.251 ± 0.239	1.355 ± 0.162	108
Putamen	0.985 ± 0.214	1.542 ± 0.262	157
Thalamus	1.173 ± 0.180	1.727 ± 0.225*	147
White matter	0.629 ± 0.125	1.205 ± 0.193**	192

Activity of MAO-B is given as mean ± SEM in nmole per min per mg protein.
* $p < 0.05$; ** $p < 0.025$, *t*-test (unpaired)

Since the increase in MAO-A activity in the AD/SDAT cases was against expectations (see Discussion), analyses of the individual cases were performed, where it was found that in all regions, the highest MAO-A activities, with some margin, could be found in 3 of the 8 cases. Even if a comparison was made between the remaining 5 patients and the controls, however, significant differences were found in the thalamus (0.256 ± 0.009 and 0.208 ± 0.021 nmole per

min per mg protein, respectively, $p < 0.05$) and in the white matter (0.091 ± 0.018 and 0.058 ± 0.006 nmole per min per mg protein, respectively, $p < 0.05$). In Fig. 1 are shown the mean MAO-A and -B activities as well as the GABA-T activities of all the cortical regions, the thalamus and of the white matter in the controls, in the 5 AD/SDAT patients with moderate changes and in the 3 patients with great changes in these enzyme activities. It can be seen that the GABA-T activity in the cortical regions and in the thalamus was lowest in the 3 AD/SDAT patients with the highest MAO-A and -B activities and highest in the controls. It can also be seen that the pattern for the MAO-A and -B activities were rather similar, both with regard to the 3 groups of individuals and the 3 brain regions shown. When the diagnoses and microscopic investigations of the different AD/SDAT cases were analysed the following observations were made. The two patients with the diagnoses AD type I and the patient with the late onset (93 years) dementia constituted the group of the three patients. The five patients all had the diagnoses SDAT (type II). The patients with late onset dementia had rather well preserved neurons otherwise no difference in the histopathological picture was seen between the groups. It can also be mentioned that the patient with late onset dementia had a pernicious anemia in her anamnesis. As mentioned under materials, histopathological investigation was missing for two out of the eight AD/SDAT cases. Removal of those two cases did not change any of the significant biochemical differences between the AD/SDAT cases and the controls (data not shown).

The three cases with more severe changes had the longest duration of the dementia disorder (9, 11,14 years) compared to the five others (2, 3, 3, 6, 7 years). Two patients in the group of three had the lowest brain weight (F, 1025;

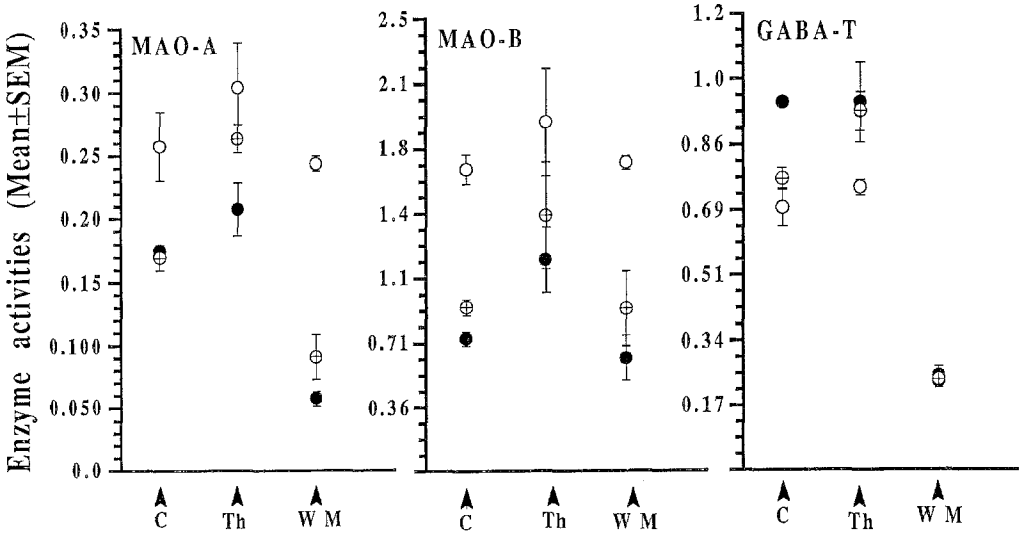

Fig. 1. Mean activities ± SEM for MAO-A, MAO-B and GABA-T for control subjects (●; n = 6) and AD/SDAT patients (○; n = 3, ⊕; n = 5) in the cortical regions, thalamus and white matter. Abbreviations: *C* Cortical regions; *Th* Thalamus; *WM* White matter

F, 1098; M, 1205 gram) compared to the five others (F, 1116; F, 1275; M, 1115; M, 1189; M, 1243 gram).

Discussion

Our findings in the present study on four cortical brain regions, three nuclei in the basal ganglia, thalamus and white matter from patients with AD/SDAT are: (a) a reduction in cortical GABA-T activities and caudate nucleus; (b) increased MAO-A activities in occipital cortex, caudate nucleus, thalamus and white matter; (c) increased MAO-B activities in the cortical regions, thalamus and white matter.

The mean reduction of the GABA-T activities found in the AD/SDAT patients in the cortical regions and the caudate nucleus was in the order of 20–30%. This result is not likely to be a result of differences between the patient and control series with regard to sex, age or postmortem time before freezing, since they were carefully matched for these parameters (Table 1). Furthermore, results from a previous study, (Sherif et al., 1991), as well as our unpublished data, suggest that age and gender do not affect brain GABA-T activity. The result is in sharp disagreement with the only report previously published on GABA-T activity in the brains of patients with AD. Thus, Aoyagi et al. (1990) found a significantly increased GABA-T activity in the occipital lobe in brain of patients with AD (510% of the control value). We have no explanation for this discrepancy, but it is notable that their activities were 10–20-fold lower than usually found (Maitre et al., 1979; White and Faison, 1980; Sherif et al., 1991). Furthermore, it is notable that they found a 17-fold increase in choline acetyltransferase activity in the AD brains, which is at variance with the typical findings of reduced activities of this enzyme throughout the brain (see Gottfries, 1990). It is difficult to draw any firm conclusion on the regional distribution of the reduction of the GABA-T activity. It is obvious from Table 2, that all the cortical regions are affected, but there is also a significant reduction in the caudate nucleus and, although not reaching statistical significance, the mean activity of the patients in the thalamus was reduced by 15%. The pathological changes in Alzheimer's disease are thought to mainly affect cortical regions, while also subcortical changes are found in senile dementia of Alzheimer type (Gottfries, 1990 a). The patient series in the present includes both diagnoses. Furthermore, when three of the AD/SDAT and three of the control brains in the present study previously were analysed by autoradiography for the occurrence of MAO-B binding sites, these were found to be generally increased throughout the brains in the patient series, supporting the notion that pathological changes in AD/SDAT brains are not always distinct regional features (Jossan et al., 1991).

There are a number of observations indicating that GABAergic systems are involved in AD. Rossor et al. (1982, 1984) and Ellison et al. (1986) reported of low cortical GABA concentrations in patients with AD and Enna et al. (1977) and Pomara et al. (1989) of low CSF GABA levels in AD patients. Furthermore,

Hardy et al. (1987) recently demonstrated a 20–30% loss of GABA neurons in cortical regions without any significant changes in subcortical regions. The activity of GAD has also been studied in brains from AD/SDAT patients and was found to be reduced in some regions of the cerebral cortex (Bowen et al., 1976; Perry et al., 1977; Davies, 1979) and in the midbrain (Davies, 1979). Thus, our results of low cortical GABA-T activity are in line with previous studies of low GABA levels and GAD activities, supporting the notion that GABAergic system is involved in AD/SDAT.

The findings of a significantly increased MAO-B activity in the cortical regions and thalamus in the AD/SDAT brains are in good agreement with previous reports (Adolfsson et al., 1980; Oreland and Gottfries, 1986; Reinikainen et al., 1988; Jossan et al., 1991). Also the relatively very high increase in the white matter (about 2-fold) is similar to that previously reported (Oreland and Gottfries, 1986). The lack of increase in the caudate nucleus and globus pallidus, was, on the other hand, unexpected. So far, however, all studies on MAO in the brains of AD/SDAT patients have been carried out on rather small series, and it seems likely that the degree of gliosis, which is supposed to cause the selective increase in MAO-B activity (see Oreland et al., 1990), might differ regionally between different patients.

The MAO-A activity has, in previous studies on AD/SDAT brains, not been found to be different from controls (Adolfsson et al., 1980; Oreland and Gottfries, 1986). Neither has MAO-A activity, in contrast to MAO-B activity, been found to change with normal aging (Fowler et al., 1980) or experimental lesioning of rat brains (Coyle et al., 1978; Oreland et al., 1980; Jossan et al., 1989). Thus, the present results with significantly increased MAO-A activities in the occipital cortex, caudate nucleus, thalamus and white matter of the AD/SDAT brains (Table 3) were unexpected. At present the heterogeneity of Alzheimer type dementia is discussed (for review see Blennow, 1990). Data indicate that early onset AD is a more pure form (type I) than the late onset form (type II). The neurochemical pathology is most pronounced in the type I form, which also has the longest duration. The finding that three of the cases had the most marked changes in all three enzyme activities investigated, is of interest as two of these cases were AD type I. The third patient with late onset dementia also had a pernicious anemia in her anamnesis. Vitamin B-12 deficiency is reported in a subgroup of SDAT (Oreland et al., 1990; Regland et al., 1991). Possibly vitamin B-12 deficiency together with high age may cause the same type of neurochemical changes as type I AD.

With regard to the increase in MAO-A activity, it shows that a severe or special type of gliosis obviously also can be reflecting an increase in this enzyme activity. An increase in MAO-B activity alone should not, according to previous experience, significantly have affected serotonin oxidation (here denoted as MAO-A activity) at the concentration used in the present study (Francis et al., 1985). Furthermore, in the white matter, the increase in MAO-A activity was, indeed, greater than that of the MAO-B activity (Fig. 1). It is of interest to note

that a regional heterogeneity among astrocytes in the central nervous system, also with regard to MAO activity, recently has been reported (Hansson, 1990). The observed increase in MAO-A activity might explain some of the inconsistencies in the literature about MAO activities in substantia nigra in brains from patients with Parkinson's disease, with reports about both mainly increased MAO-A and -B activities, respectively (Jellinger and Riederer, 1984; Riederer et al., 1989).

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