Biochemical Pharmacology, Vol. 38, No. 4, pp. 555–561, 1989.
Printed in Great Britain.

0006-2952/89 $3.00 + 0.00

COMMENTARY

MONOAMINE OXIDASE, BRAIN AGEING AND DEGENERATIVE DISEASES

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Oxidative deamination of primary monoamines by the mitochondrial enzyme monoamine oxidase (MAO, EC 1.4.3.4) produces NH_3, aldehydes and H_2O_2, agents with established or potential toxicity. In the brain, MAO is active in both neurons and glial cells.

In 1968, Johnston discovered that MAO exists in two forms, termed MAO-A and MAO-B, with different substrate specificities and inhibitor sensitivities [1]. Recent work has indicated that the two forms of MAO have overlapping, rather than absolute, specificities. Thus, 5-hydroxytryptamine (5-HT), which has generally been regarded as being a specific substrate for MAO-A, has been shown to also be a substrate for rat brain MAO-B, but with a much higher K_m value and a much lower maximum velocity (V) than those of the A form [2]. Conversely, 2-phenylethylamine (PEA) is a substrate for MAO-A, but with a higher K_m value and a lower V than the corresponding values for MAO-B [3].

The purpose of this paper is to review the changes in brain MAO activities in relation to age, both in animals and in humans, as well as the changes occurring in dementia of the Alzheimer type and in Parkinson's disease. It is also to debate whether or not the degeneration processes associated with age and Alzheimer's and Parkinson's diseases may be seen, at least in part, as the result of an oxidative stress to which an exaggerated formation of H_2O_2 by MAO without concomitant increase in H_2O_2-detoxifying enzymes would contribute.

The appearance of extrapyramidal disturbances in Alzheimer's disease [4] and the gradual loss of intellectual functions in Parkinson's disease [5] may indicate an overlap between these two pathologies. As recent studies of subjects with Down's syndrome and patients with Alzheimer's disease have revealed previously unexpected similarities between the two illnesses [6–9], the MAO changes in Down's syndrome will also be compared to those observed in the other diseases. Many studies have involved a possible correlation between CNS diseases and the levels of MAO activity in platelets [see Ref. 10 for review], and thus the available data on MAO activity in this tissue also will be commented on briefly.

MAO in brain of young and old rats

MAO activities in brain of male old Wistar rats, aged 23–26 months, were measured by Cao Danh *et al.* [11] and compared with those of male young animals of 3 months.

In the brain of both young and old rats, 5-HT is metabolized almost only by MAO-A and PEA by MAO-B, even though for the latter a small contribution by the A form cannot be excluded [2]. When enzyme activity was expressed per mg of tissue and per mg of protein, a significant increase was found in the brains from old rats with PEA (25 and 16% respectively) and a small but significant decrease with 5-HT (−4 and −8% respectively). Thus, MAO-B activity increases in the whole brain of old rats, whereas that of MAO-A decreases. MAO activity was also measured by the same authors in seven different brain areas from old and young rats. When calculated per mg of tissue, 5-HT deamination was found to be reduced slightly but significantly in cerebral cortex (−6%), midbrain (−11%) and hypothalamus (−9%) from the old rats, whereas no significant change was observed in hippocampus, striatum, brainstem and cerebellum. For PEA deamination, a significant increase was found in cerebral cortex (+27%), hippocampus (+27%), midbrain (+10%), striatum (+29%), hypothalamus (+11%) and cerebellum (+11%) from the old rats, but there was no significant difference between the activities in brainstem from young and old rats. Since a significant increase in protein content was observed in almost all brain areas from the old rats, calculation of MAO activity per mg of protein tended to reduce age-related differences where MAO activity was increased with age and tended to increase the differences where MAO activity fell with age. To summarize, in old rats MAO-A activity was decreased significantly in all the regions studied except in cerebellum, where it was unchanged, whereas MAO-B activity increased in all the areas studied except in brainstem, where it decreased. The results of Cao Danh *et al.* [11] are in good accordance with those of Leung *et al.* [12] who also used Wistar rats. Thus, the regional changes in MAO-B activity were not dependent on those in MAO-A activity. This suggests that the mechanisms which alter the activities of the two forms are unrelated.

In old Sprague–Dawley rats, Strolin Benedetti and Keane [13] also found an increase of whole brain MAO-B activity and a decrease of whole brain MAO-A compared with the corresponding activities in young rats. Also, in this strain the MAO-B activity increased with age in all regions, except the brainstem; the MAO-A activity fell or did not change in

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all regions, except the cerebellum where it increased by 17%. Kinetic studies indicated that the V of MAO-B was increased in whole brain homogenates of old rats, whereas the K_m was unaltered. Following a crude separation of intrasynaptosomal and extrasynaptosomal mitochondria, the increase in MAO-B activity seemed to be restricted to the extrasynaptosomal mitochondrial fraction of the brain of old rats, whereas the reduction in MAO-A activity was found only in the intrasynaptosomal mitochondrial fraction.

When rats are transected on one side of the brain, losing monoamine neurons, MAO-B but not MAO-A activity is increased, although no changes in MAO activity occur on the unoperated side [14]. The microglia appears to be the major component of extraneuronal growth following neuronal loss. These glial cells seem to contain predominantly MAO type B. Thus, reactive microgliosis following hemi-transection and therefore neuronal loss is consistent with the observed increase in MAO-B activity. Peng and Lee [15] have shown that there is a decrease in the concentration of neurones in the cerebral hemispheres and cerebellum but not in the brainstem of 24- to 30-month-old rats, as compared with young adult rats. Such a resistance of the rat brainstem to neurone loss with age is consistent with the lack of any effect of age upon the MAO-B activity of the medulla oblongata. Thus, the age-dependent increases in MAO-B activity, reviewed above, may reflect glial cell proliferation accompanying neurone loss, and the fall in MAO-A activity may reflect a preponderance of that form of the enzyme in those neurones that degenerate with age.

Changes in human brain MAO with ageing

Robinson [16] studied the changes in MAO activities in brain specimens obtained at autopsy from patients who died from a variety of illnesses. MAO activity was assayed with benzylamine (Bz) as substrate. There was a positive correlation of hindbrain (rhomboencephalon) MAO-B activity with age. This correlation of age with hindbrain MAO is particularly intriguing because the increase in enzyme activity began in middle age when the incidence of serious depressive illness also rises [17]. Robinson [16] also determined whether a similar relationship of enzyme activity to age held for the brain cortex and for specific subcortical regions. Of the thirteen brain specimens assayed, six came from subjects younger than 45 years of age and seven from subjects over 45 years of age. For most of the areas, the mean MAO-B activity appeared to be greater for the older group than for the younger one. Thus, the MAO-B–age relationship observed for whole hindbrain tissue seemed to hold for a variety of discrete brain areas as well.

An increase of MAO-B activity in human frontal cortex with age was shown by Oreland and Fowler [18]. They studied the enzyme activity from twelve deceased patients of age range 2–95 years, all without any history of psychiatric illness. No apparent change in the activity towards 5-HT with age was found, but there was an increased activity towards Bz with age. The dependence of the activity of human brain MAO-B, but not of MAO-A, on normal ageing was confirmed by Carlsson *et al.* [19] and Gottfries *et al.* [20]. They found a positive correlation between age and MAO-B activity in cortex gyrus cinguli, hippocampus, caudate and hypothalamus.

An extensive study on this subject has been carried out by Fowler *et al.* [21] who investigated the effect of age on both MAO-A and -B activities in twenty-three different brain regions. They divided the samples into two groups: under 65 years (N = 8) and over 65 (N = 9). There were no differences in MAO-A activities between the two groups in twenty-two out of twenty-three brain regions (the right hippocampus being the exception), but the MAO-B activities were significantly higher in the over-65 group than in the under-65 group in seventeen out of twenty-three brain regions. Large increases in the activities of MAO-B with age were seen in the hypothalamus, thalamus, the nigrostriatal system (caudatus, putamen and substantia nigra), and the limbic system (hippocampus, amygdala and, to a lesser extent, the cortex gyrus cinguli, which, although a cortical region, belongs to the limbic system). The MAO-B increase with age was considerably less marked in the cortical regions tested (frontal and precentral cortices, also the cortex gyrus cinguli). Interestingly, of the brainstem structures, there was a small increase with age in the pons, but no increase in the medulla oblongata.

An increased MAO-B activity assayed at a fixed substrate concentration could be due to: a decreased K_m value towards the substrate, an increased molecular turnover number (MTN) (mol of substrate deaminated/mol MAO-B/min) of the enzyme towards the substrate, an increased concentration of available enzyme active centres or a combination of these effects. Fowler *et al.* [21] also studied the nature of the MAO-B selective increase in human brain with age in different brain regions. The differences in activities appeared to be due to differences in the V values rather than to K_m differences. Selective titration of MAO-B active centres was performed by using the irreversible acetylenic inhibitor J-508 (2,3-dihydro-*N*-methyl-*N*-2-propynyl-1*H*-inden-1-amine) which appears to interact directly with the active center of MAO-B, without any observable non-specific binding to other sites [22]. An increased concentration of this enzyme form with age was found in all brain regions examined, except the medulla oblongata, and there was a very good correlation between the V value and the MAO-B concentration for all brain regions. Therefore, the increased MAO-B activity observed with age is not due to an increased MTN of the enzyme. The MTNs of the MAO-B were calculated as V/MAO-B concentration. The mean values of five [thalamus (left and right), caudatus (right), hippocampus (left and right)] out of the six regions tested were found to vary from 257 to 304. The mean value for the medulla oblongta (181 ± 7) was significantly lower than those for the other five brain regions. The MAO-B of the medulla oblongata may possibly be under different control with respect to that enzyme in the rest of the brain, since not only does it display a lower MTN towards Bz, but also because it is not affected by age.

In contrast to this behaviour of MAO in human brain, there appear to be no significant age-related

changes in the activity of the enzyme in human platelets [23].

Changes in brain and platelet MAO activities in dementia of the Alzheimer type

Adolfsson *et al.* [24] determined the MAO activity in the brain (hypothalamus, caudate nucleus, hippocampus and cortex gyrus cinguli) from fourteen patients with dementia of the Alzheimer type and compared the results to sixteen controls matched for age and sex. Brain MAO-B activity was significantly higher in the dementia group in hippocampus and cortex gyrus cinguli and bordered significance in the two other areas. However, a recent study by Oreland and Gottfries [25] showed a significant increase of MAO-B (about 20%) in the caudate nucleus from the patients with Alzheimer dementia as compared with age-matched controls. According to the same authors [25], data on MAO-B in white matter show that, as in most of the specific regions containing mainly gray matter, there is a significant increase of MAO-B activity with age. When the comparison was carried out between patients with Alzheimer dementia and age-matched controls, a large increase (about 71%) in the MAO-B activity in the white matter was observed. The increase of MAO-B activity in white matter seemed to be due to an increase in V, while there were no changes in the K_m values.

Adolfsson *et al.* [24] measured MAO activity in platelets from eleven patients who fulfilled the criteria of dementia of the Alzheimer type as well as in platelets of a control group of eleven healthy volunteers, matched for age and sex. Only the B form of MAO is present in human platelets [26]. The MAO-B activity was significantly higher in platelets of patients with dementia of the Alzheimer type with respect to controls. While the selective increase in the MAO-B activity in the brain tissue can be explained by a higher neuronal loss and a higher proliferation of extraneuronal tissue in this disease than in normal ageing, the cause for the increase in platelet MAO activity is still a matter for speculation [20, 27]. The disease may be associated with a generalized increase in MAO-B activity, although results from other tissues are necessary to confirm such a view. In any case, the finding of an increased MAO activity in platelets suggests that the effects of the disease are not confined to brain tissue [7].

In a recent paper Reinikainen *et al.* [28] provided further confirmation that there was no difference in MAO-A activity from different brain areas between patients with senile dementia of the Alzheimer type and controls. Concerning MAO-B activity, they found an increase, especially in cortical areas, which was significant in parietal cortex and in thalamus. The same authors found no increase in MAO-B activity in cortical areas from patients with vascular dementia.

Although the biological significance of the increased MAO-B activity is uncertain, it appears nevertheless to be of interest to try selective MAO inhibitors in the treatment of Alzheimer dementia and senile dementia.

Changes in brain MAO activity in Parkinson's disease

According to Lloyd *et al.* [29] the MAO activity, measured with tyramine as substrate in several brain regions from L-dopa-treated or non-treated Parkinsonian patients, was not significantly different from control levels. The MAO activity of the cerebellar cortex was an exception in that it was increased significantly (by 70%) as compared to the controls. However, as tyramine is a substrate of both forms of MAO, and as selective inhibitors were not used to inhibit one or the other form of MAO, it is impossible to know which form was increased in the cerebellar cortex and whether the lack of changes in the other brain structures really reflected the absence of changes in MAO-A and -B activities or was due to an increase of one form of MAO associated with a decrease of the other form.

In 1983, Riederer *et al.* [30] found an increase of MAO-A (5-HT) and -B (PEA) activities in the substantia nigra from patients with severe Parkinsonism. The same group in 1984 [31] published comparative data on MAO activity in different brain regions, including substantia nigra, from seven cases of benign Parkinson's disease and from eleven controls, who were matched for age and had received no psychotropic drug treatment. The Parkinsonian patients were on combined long-term L-dopa treatment with additional administration of dopaminergic agonists, amantadine or neuroleptics but not MAO inhibitors. In both Parkinsonians and controls, MAO-B (PEA) activity was much higher than MAO-A (5-HT) activity in the four regions studied: caudate nucleus, putamen, substantia nigra and frontal cortex. When compared to controls, no significant changes in the MAO-B activity were seen in the caudate nucleus, substantia nigra and frontal cortex from Parkinsonian patients, whereas an increase (about 40%) was observed in putamen. The lack of any increase of MAO-B activity in substantia nigra of Parkinsonian patients in this work contrasts with previous results reported by this group [30]. Concerning MAO-A activity, no changes were observed in Parkinsonian patients except in substantia nigra, where a significant increase in 5-HT deamination (of about 90%) was found.

It is necessary to be extremely careful in discussing data obtained on brain MAO activity from Parkinsonian patients, since they are usually on treatment with L-dopa plus an inhibitor of peripheral L-aromatic amino acid decarboxylase such as carbidopa or benserazide. Several authors have reported data showing an effect of these compounds on MAO, both in humans and in animals. Zeller *et al.* [32] found that platelet MAO is reduced slightly in untreated Parkinsonian patients as compared with age-matched controls, and that treatment with L-dopa induces a further reduction of platelet MAO activity. Naoi and Nagatsu [33] found that L-dopa slightly inhibits the activity of MAO-A and MAO-B from human tissues *in vitro* in a noncompetitive manner towards kynuramine as substrate.

Reports from studies with rats have suggested that the administration of L-dopa may influence, sometimes in an opposite way according to factors such as acute or chronic administration, the activity

of MAO in certain tissues [34, 35]. A recent study of Callingham and Lyles [36] was designed to investigate whether or not increases in MAO specific activity that follow chronic treatment of rats with L-dopa could be modified by benserazide. Rats received L-dopa (250 mg/kg/day, s.c.) and benserazide (40 mg/kg/day, i.p.), either alone or in combination, for 10 days. The activity of MAO in homogenates of heart, kidney, liver and brain was measured with 5-HT and Bz as substrates. The significant increases in MAO specific activity seen in heart and kidney following L-dopa treatment could be reduced or prevented by benserazide. Rat brain MAO was largely unaffected by any of the drug treatments studied, except for a small reduction in Bz metabolism in benserazide-treated rats, which just reached the level of significance. Carbidopa produced an increase of cerebral cortical and striatal MAO type-B activity of about 40% several hours after a single i.p. administration to rats, with no effect on MAO-A [37, 38]. However, carbidopa does not appear to affect MAO *in vitro* [33]. The increase of striatal MAO-B activity induced by carbidopa may counteract or add instability to the results of levodopa treatment; moreover, if Parkinson's disease results from, or is perpetuated by, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-like toxins which also require MAO-B activation [39], the use of carbidopa may enhance neurotoxicity.

As well as being a substrate for MAO-B, which results in its activation, MPTP is also an irreversible inhibitor of that enzyme *in vitro* [40, 41]. However, administration to mice of a dose of MPTP that markedly decreased motor activity did not affect MAO-B activity *ex vivo* [42]. The lack of any depression of MAO-B activity in Parkinsonian patients makes it possible that exogenous compounds could be transformed into neurotoxins by MAO-B and may be involved in the etiology of Parkinson's disease.

Activity of MAO in Down's syndrome

No published data seem to be available concerning brain MAO activity in Down's syndrome. The activity of this enzyme has been measured in platelets from subjects with Down's syndrome as well as controls by Benson and Southgate [43]. Platelets were obtained from twenty-two children with primary trisomic Down's syndrome and from twenty-two controls who were matched for age (mean 3.9 years; range 1.07 to 7.8 years). MAO activity was measured using kynuramine as the substrate. Platelet MAO activity was found to be significantly lower in subjects with Down's syndrome than in controls.

A more recent and complete study was carried out by Fowler *et al.* [44] on platelet-rich plasma samples from 183 healthy volunteers (19–63 years) and 16 Down's syndrome patients (14–64 years), using tyramine, PEA and tryptamine as substrates. The patients with Down's syndrome appeared to have a significantly lower activity of MAO than the controls, both for males and females. The same authors also studied the kinetic properties of the MAO from both controls and Down's syndrome patients, using tryptamine as the substrate. The K_m values in the patients and controls appeared to be rather similar, the difference in activities between the two groups being due to a difference in the V values. Although the Down's syndrome patients had higher platelet concentrations in the platelet-rich plasma, the total deaminating capacity of the plasma was lower in these patients than in the controls.

Concluding remarks

In conclusion, it appears that brain MAO-B increases with age in both animals and humans. This increase is accentuated in patients with dementia of the Alzheimer type with respect to age-matched controls, whereas this does not seem to be the case for patients with vascular dementia. In Parkinsonian patients, there is a discrepancy between the published data, with increased levels of cerebral MAO or no significant changes being reported.

In the case of patients with Down's syndrome, the decrease of MAO activity in their platelets does not strengthen the hypothesis of similarities between patients with Alzheimer's disease and Down's syndrome. The levels of lipid peroxides seem to be increased significantly in the blood of patients with Down's syndrome [45], supporting the hypothesis of increased oxidative stress in this disease. However, the decreased levels of platelet MAO suggest that hydrogen peroxide produced by this enzyme does not contribute to such an increase.

The increase in MAO-B on ageing may be associated with the glial cell proliferation that accompanies neuronal loss. This would be consistent with the observation, discussed earlier, that the increase in the activity of this enzyme was confined to extrasynaptosomal mitochondria and with the microglia containing predominantly the B-form of MAO. The less consistent changes in MAO-A activities may reflect neuronal loss since the relative proportions of the two forms of the enzyme appear to vary in different types of aminergic neurones and different brain regions [46–48]. Since the exact proportions of the two forms in microglial cells have not been determined, it is also possible that a small loss in MAO-A activity in some regions, due to neuronal degeneration, may be balanced by an increase in that form in the glial cells. The situation is clearly different from that in rat heart where the MAO-A activity increases significantly with ageing due to a decrease in the rate of enzyme degradation [49].

The biological significance of an increased activity of brain and/or platelet MAO-B is uncertain. However, it is interesting that the age of animals appears to be a critical factor in the neurotoxicity of MPTP, a compound bioactivated to a neurotoxic agent by MAO-B [50].

In the old rat, following the increase of brain MAO-B, Strolin Benedetti *et al.* [51] studied whether the brain enzymes involved in detoxication processes of the MAO-generated compounds are also increased. They found that aldehyde reductase and aldehyde dehydrogenase were also increased with age, and the same phenomenon was observed with glutamine synthetase. Therefore, the activity of the key enzymes for detoxifying aldehydes and NH_3 produced by MAO increases concomitantly with MAO-B activity on ageing. The possible compensation for the consequences of the increase of brain MAO with age is more critical in the case of

H_2O_2, since catalase, glutathione peroxidase and glutathione reductase do not change significantly in brain of old rats compared with young controls. Moreover, glutathione levels significantly decrease in the brain of old rats. Thus, a greater sensitivity to oxidative damage arising from amine oxidation might be expected to accompany ageing, and this might be a particular problem in combination with drugs which elevate the concentrations of amines that are substrates for MAO-B without inhibiting that enzyme. Such treatments might include L-dopa therapy and the use of antidepressant uptake inhibitors that affect the transport of noradrenaline and dopamine, both of which are substrates for both forms of MAO in the human brain [52, 53]. In the latter case, however, the mild inhibitory action of tricyclic antidepressants toward MAO-B [54] may reduce such an effect.

The increase of glucose-6-phosphate dehydrogenase observed in rat brain with age may be only a partial compensation, if any, for neurotoxic processes enhanced by the increase in MAO activity. Finally, it must be kept in mind that further reactions between endogenous compounds and the agents produced by MAO, and increased with age, might be favoured, such as condensation of aldehydes with amines [54] or formation of hydroxyl radicals by H_2O_2 through the Fenton or the Haber–Weiss reaction [55, 56], which may also contribute to neurotoxicity.

Administration of classical and non-selective MAO inhibitors, such as nialamide, in people with Down's syndrome has been reported to produce increased motor activity and quickened mental and physical reactions, but no convincing improvement in intellectual performance [43]. In relation to the increase in MAO-B activity, there is some rationale for the administration of selective MAO-B inhibitors for the treatment of dementia and Parkinsons' disease [see Ref. 57 for review]. According to Gottfries [58], investigations with selective MAO inhibitors are in progress for the treatment of dementias, and *l*-deprenyl, a selective MAO-B inhibitor, has been found recently to improve episodic memory and learning task requiring complex information processing in patients with dementia of the Alzheimer type [59]. *l*-Deprenyl is also under investigation for altering the course of early Parkinson's disease by slowing its progression in patients not treated with L-dopa [60]. Finally, a recent publication refers to testing of a combined treatment with *l*-deprenyl and the antioxidant vitamin E in Parkinson's disease [61]. The report that combined therapy of Parkinsonian patients with *l*-deprenyl plus L-dopa significantly prolongs the life expectancy as compared with treatment with the latter compound alone has been interpreted in terms of the generation of neurotoxic metabolites as a consequence of the activity of MAO-B on dopamine [62].

Acknowledgements—The authors are grateful to Prof. K. F. Tipton, Trinity College, Dublin, for his helpful advice, and thank Mrs L. Magné for typing the manuscript.

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