Age Related Changes Regarding Monoamine Oxidase (MAO) Activity in the Human Brain¶

İNSAN BEYNİNDE MONOAMİNO OKSİDAZIN (MAO) YAŞLA DEĞİŞİMİ

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Summary

In order to explain mental impairment in the elderly, various physiological and pathological parameters have been investigated. Based on an increased amount of research on cerebral biogenic amines metabolisms during ageing , we aimed to determine and compare Monoamine Oxidase (MAO) activity in various parts of the human brain such as the prefrontal cortex responsible for high intellectual capacity, temporal cortex associated with short term memory and learning and the cerebellum related to motor learning and classical conditioning.In this study, a significant correlation was found between prefrontal cortex MAO activity(41.48±8.34, 56.93+21.58, 48.33±15.31 nmol/mg protein / hr respectively for 0-20, 21-50 years and over 50 years) of age. There was no significant positive correlation between MAO activity and age (42.40±9.1 for 0-20 years, 53.11±16.43 for 21-50 years and 60.58 ±20.22 nmol/mg protein /hr over 50 years) in temporal cortex. However, in the prefrontal and the temporal cortex, comparison of 0- 20 years age group with 21-50 and over 50 years group reveals a significant increase in MAO activity. Increase of MAO activity in these brain regions may be a factor which contribute to development of mental impairment and forgetfulness in aged population. On the other hand, in the cerebellum, no significant correlation was determined between ageing and MAO activity (40.88±11.61, 49.85±23.35, 39.33±14.87 nmol/mgprotein/hr).

Key Words: Monoamine oxidase, Human brain, Aging

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Özet

Yaşlı kişilerdeki mental fonksiyonlardaki azalmayı açıklamak için bir çok fizyolojik ve patolojik parametreler incelenmiştir. Yaşlılıktaki serebral biyojen amin metabolizma araştırmalarının giderek artmasına dayanarak Monoamin oksidaz (MAO) aktivitelerini; yüksek entellektüel kapasiteden sorumlu olan prefrontal korteks, kısa süreli bellek ve öğrenme ile ilişkili olan temporal korteks ve motor öğrenmenin ve klasik koşullanmanın gerçekleştiği serebellumda belirlemeyi ve karşılaştırmayı amaçladık.

Yaptığımız bu çalışmada, yaşla prefrontal korteks MAO aktivitesi arasında anlamlı bir ilişki bulundu (0-20, 21-50, 50 yaş üstü için sırasıyla 41.48±8.34, 56.93±21.58, 48.33±15.31 nmol/mg protein/saat).Temporal kortekste yaşla MAO aktivitesi arasında anlamlı bir korelasyon yoktu. (0-20 yaş için 42.40±9.1, 21-50 yaş için 53.11±16.43 ve 50 yaş üstü için 58±20.22 nmol/mg protein/saat).Ancak prefrontal ve temporal korteksin 0-20 yaş grubunun MAO aktiviteleri 20-50 yaş grubu ve 50 yaş üstü ile karşılaştırıldığında anlamlı bir artış olduğu görüldü. Bu beyin bölümlerinde yaşlı kişilerdeki MAO aktivitesinin artması unutkanlık ve mental kapasitedeki azalmaya neden olan faktörlerden birisi olabilir. Serebellumda ise yaş ile MAO aktivitesi arasında anlamlı bir korelasyon bulunamadı (0-20, 21-50, 50 yaş üstü için sırasıyla 40.88±11.6, 49.85±23.3, 39.33±14.87 nmol/mgprotein/saat).

Anahtar Kelimeler: Monoamino oksidaz, İnsan beyni, Yaş

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Recently there has been a growing interest in cerebral biogenic amines and their metabolism. Cerebral amines may play an important role in various pathologies such as schizophrenia, depression, mania, Parkinson's disease, Alzheimer's disease and dementia. There is also evidence that they may be involved in the process of physiological ageing. The metabolic product of biogenic amines, namely 5-hidroxy indole acetic acid (5 HIAA), is found to be elevated in the cerebrospinal fluid of elderly people (1). The increase of cerebral biogenic amines metabolites in subjects might be secondary

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to an increase in the activity of monoamine oxidase(MAO), a flavin adenine dinucleotide (FAD) containing major intracellular enzyme responsible for degrading biogenic amines such as serotonin, dopamin, epinephrine and norepinephrine by oxidative deamination in various tissues throughout the body including blood, platelets, liver, kidney, intestines placenta and most importantly in brain and nervous tissue (2,3).

MAO (E.C.1.4.3.4.) selectively catalyses the oxidation of biogenic amines by the reaction (4):

$RCH_2NH_2 + O_2 + H_2O \rightarrow RCHO + NH_3 + H_2O_2$

There are at least two known MAO isoenzymes (A and B), Type B MAO is found mostly in the mitocondria of glial cells in the brain(4). During the process of ageing it could be that MAO responds to environmental changes or it is also possible that the MAO expressing gene is regulated by transcriptional factors involved in this process (4). The alterations in brain MAO activity may also account for the decline in the norepinephrine and dopamine content of the human central nervous system observed with age (5).

Based on various investigations on cerebral biogenic amine metabolism, the objective of this study has been to determine and compare MAO activity of dıfferent age groups in various parts of the human brain such as the prefrontal cortex, temporal cortex and cerebellum; and thus help to clarify the linkage between MAO and the process of ageing.

Materials and Method

Human brain tissue specimens were obtained within the first 16 hours from 40 postmortem cases without any neurological findings, ages ranging from 4-84 years. The brain specimens were selected from the routine autopsy materials of the departement of Forensic Medicine of Aegean University. The various causes of death are shown in Table 1 and the dıfferent age groups are shown in Table 2. Prior to death, cases of acute myocardial infarction had been treated with heparine, acetyl salycilic acide and isosorbide dinitrate, whereas the remaining cases had not received any treatment. In each case, specimens were dissected from 3 different regions of the brain, namely the prefrontal cortex, the temporal cortex and cerebellum; immediately frozen and stored at -40^{o}C no longer than one month and finally homogenized and assayed.

Table 1. Causes of death

Causes of Death	Women	Men	Total
Acute myocardial infarction	1	8	9
Travma	1	7	8
Stabbing	-	6	6
Gunshot and explosion	-	4	4
Others	2	11	13
Total	4	36	40

Table 2. Age groups

Age Groups	Women	Men	Total
0-20	-	5	5
21-50	3	20	23
Over 50	1	11	12
Total	4	36	40

MAO activity was determined fluorometrically by the modified Kraml technique (1965) (7) utilizing kynuramine dihydrobromide as substrate and measuring 4 hydroxyquinoline production. The standard assay mixture consisting of 50 μM potassium phosphate buffer (pH:7.4) 0.1μM kynuramine and 50-100 μgr enzyme in a final volume of 3.0 ml was incubated at 37°C during 30 minutes. The reaction was stopped by the addition of 1 ml 4 N NaOH. The fluorescence was measured at an emission wavelength of 385 μm and excitation wavelength of 318 μm. Activity was expressed as nmol of 4-hydroxy quinoline formed per hour per mg protein at 37°C (7).

Tissue protein was assayed by the Lowry method (8). Statistical analysis was performed with the one way ANOVA test and Duncan's Multiple range test.

Results

Changes in the MAO activity of the prefrontal cortex, temporal cortex and cerebellum in various age groups are presented in Figure 1.

The comparison of the 3 different age groups with respect to prefrontal cortex MAO activity (41.48±8.34, 56.93±21.58, 48.33±15.31 nmol/mg protein/hr respectively for 0-20, 21-50 and over 50 years of age respectively) shows an elevation in MAO activity with ageing ($p<0.01$, $r=0.405$) (Figure 2). There was a positive correlation be-

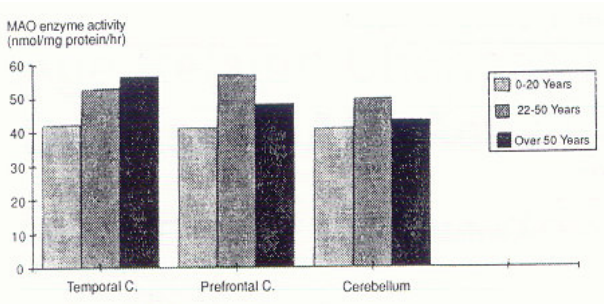

Figure 1. Prefrontal cortex, temporal cortex and cerebellum MAO activity in different age groups.

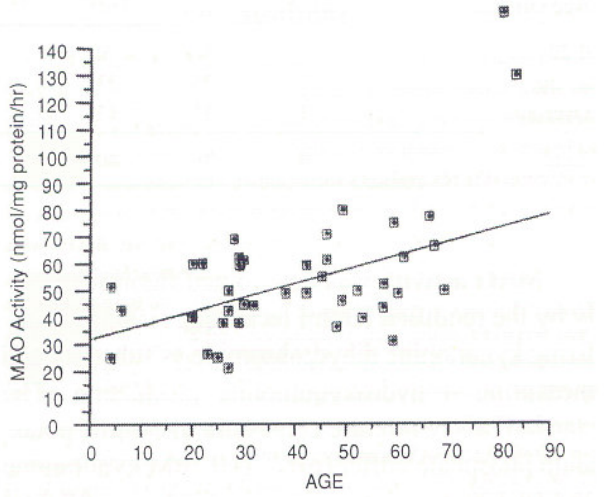

Figure 2. Human brain prefrontal cortex MAO activity regarding to age (r=0.405, y=32+0.46x).

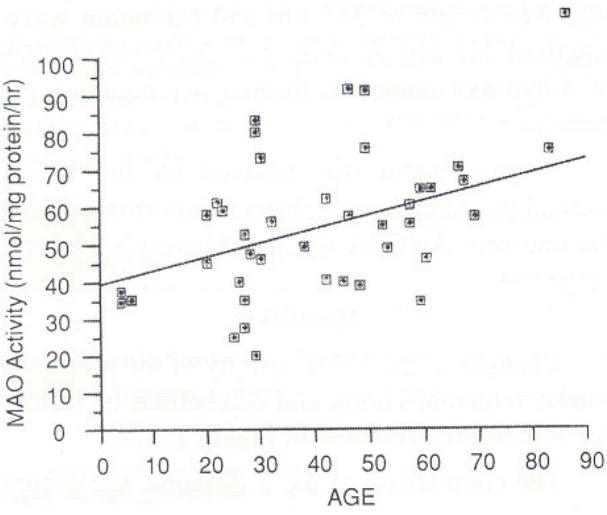

Figure 3. Human brain temporal cortex MAO activity regarding to age (r=0.23, y=39.5+0.33x).

tween prefrontal cortex MAO activity and ageing. Comparison of group 1 with group 2 and 3 shows a significant increase in MAO activity ($p<0.01$). On

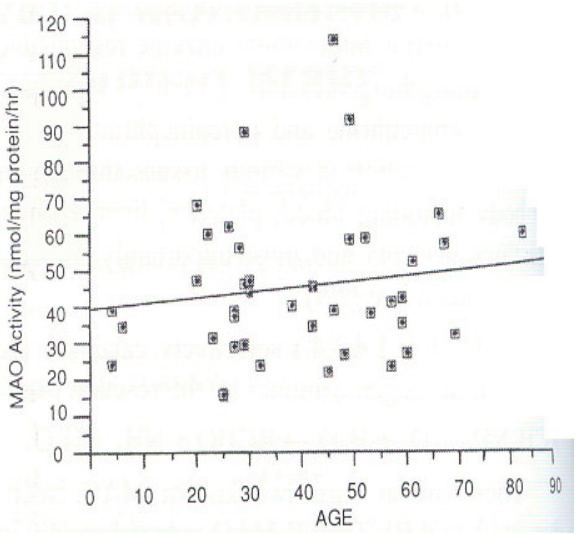

Figure 4. Human brain cerebellum MAO activity regarding to age (r=0.12, y=39+0.13x).

the other hand, no significant correlation can be noted while comparing groups 2 and 3. In figure 3 the correlation between temporal cortex MAO activity (42.40±9.1 for 0-20 years, 53.11±16.43 for 21-50 years and 60.58 ±20.22 nmol/mg protein/hr over 50 years) and ageing can be observed.There was no significant correlation between temporal cortex MAO activity and ageing can be observed ($p < 0.5$ r=0.23) (Figure 3). But; similar to prefrontal cortex comparison of group 3 and group 2 with group 1 applying Duncan's multiple range test, also reveals a significant increase in MAO activity ($p< 0.01$).

Cerebellum MAO activity does not manifest a linear increase during ageing (40.88±11.61, 49.85±23.35, 39.33±14.87 nmol/mgprotein/hr) ($p<0.5$, r=0.12) (Figure 4).

Discussion

During physiological ageing, changes in brain metabolism has been throughly investigated with special emphasis on biogen amines and MAO, an enzyme responsible for their degradation. The objective of these investigation has been to clarify the mecanisms underlying the decline in intellectual capacity progressing with age.

In general, our findings are in concordance with other investigators pointing to an elevation of MAO activity with age. D.S. Robinson et al (1), Goodnick P. and Gershon S.(1984) (9) have indicated that there is an elevation in MAO activity during ageing. Sparks D.L. (10) and Gottfries C.G.(11) have declared that MAO activity increas-

es in the temporal and frontal cortex during ageing.

In the aging brain there is a loss of neurons compansated for by the proliferation of glial cells (Knoll J., 1985) (12). Because of the increased MAO-B activity present in the glia, total MAO activity rises. It has also been shown by Mann et al. (13), Oreland et al. (14) and Kornhuber J. et al. (15).

Our results have indicated an increase in MAO activity with age, an outstanding elevation was noted especially in the prefrontal cortex which is responsible for high intellectual capacity. Various neurotransmitters, neuropeptides and genetic factors all have important roles in the cognitive process (Gottfries C. G., 1990) (11). Decrease of MAO activity in the prefrontal cortex and the cerebellum after 50 years of age may also be due to these factors. Fanchamps A.(1991) (16) claimed that in physiological aging mental impairement occurs when elderly people cease to use their brains.

In the temporal cortex which is related short term memory and learning, there was no correlation between MAO activity and age; but when the young age group (0-20 years old) was compared with the two older groups, a significant increase in MAO activity was observed. Since learning is not possible without memory, such an increase in MAO activity in the young group is of importance. In accordance with our findings S. Benedetti (17) and Gottfries (11) have stressed that during ageing MAO enzyme activity increases in regions of the brain related to problem solving.

Oxidative deamination of primary MAO produces NH_3 and H_2O_2, agents with established or potential toxicity (Strolin Benedetti and Dostert 1989) (18), (Benzi G., Moretti A,1995) (19). This may contribute to brain tissue injury and lead to mental impairment.

Based on our findings it may be stated that there is a prominent relationship between prefrontal cortex MAO activity and ageing. This brain region play an important role on high intellectual capacity like problem solving. In the temporal cortex, responsible for learning and short term memory, there was no any significant correlation between MAO levels and age; but the young group's MAO levels are higher than the older's. In the cerebellum which is responsible for motor learning and classical conditioning, there was no correlation between MAO actıvıty and age.

We can conclude that increasing of MAO activity in these brain regions may be a factor that contribute to development of mental impairment and forgetfulness in aged population. However, to make more accurate conclusions, there is a need to perform this study in more standardized groups.

A promising research area in the future is likely to be based on MAO inhibitors and their role in the regulation of cerebral biogen amine metabolism during physiological aging.

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