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VISUALIZATION OF MONOAMINE OXIDASE IN HUMAN BRAIN

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Monoamine oxidase (MAO; EC: 1.4.3.4) is a flavin containing enzyme which exists in two subtypes, MAO A and MAO B. MAO A and B are different gene products and they also differ in their substrate and inhibitor selectivities and their cellular localizations. In human brain MAO B predominates (B:A = 4:1) and is largely compartmentalized in cell bodies of serotonergic neurons and in glia. Many studies of human brain MAO B post mortem report that MAO B increases with age and in neurodegenerative disease [1]. This is consistent with investigations showing that the number of glial cells increases with age in the normal human brain [2] and in neurodegenerative disease.

As an initial step in the investigation of the feasibility of detecting and tracking neurodegenerative processes in the living human brain, we measured brain MAO B in normal healthy subjects (n=21; age range 23-86; 9 females and 12 males; non-smokers). The studies followed the guidelines of the Human Subjects Research Committee at Brookhaven National Laboratory and subjects gave informed consent after the procedures had been explained to them. We used PET and deuterium substituted [^{11}C]L-deprenyl ([^{11}C]L-deprenyl-D2) [3]. MAO B was assessed using a model term λk_3 which is a function of MAO B activity. A blood to brain influx constant (K_1) which is related to brain blood flow was also calculated. Regions of interest were occipital cortex, frontal cortex, cingulate gyrus, parietal cortex, temporal cortex, pons, thalamus, basal ganglia, cerebellum and global regions.

The regional distribution of MAO B was highest in the basal ganglia and the thalamus with intermediate levels in the frontal cortex and cingulate gyrus and lowest levels in the parietal and temporal cortices and cerebellum. The model term λk_3 showed a significant increase with age ($p<0.004$) in all brain regions examined except for the cingulate gyrus (with a trend for the parietal cortex). The results of correlation analysis for the global region is shown in Figure 1A. The same patterns remained when the correlation analysis was performed separately for males and females.

[^{11}C]L-Deprenyl-D2 has tracer characteristics which allow a plasma to brain transfer constant, a model term which is related to blood flow, to be extracted from dynamic PET data. In contrast to λk_3 which increased with age, K_1 significantly ($p<0.01$) decreased in all brain regions except for the pons and the cerebellum. The highest correlation coefficients were in the cingulate gyrus, the frontal cortex, the temporal cortex and the parietal cortex consistent with other studies. Individual data for K1 for the global region vs age is shown in Figure 1B.

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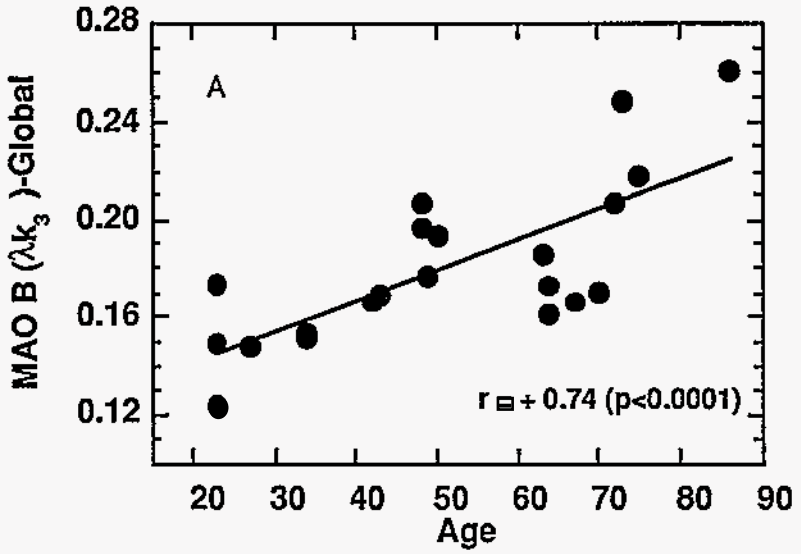

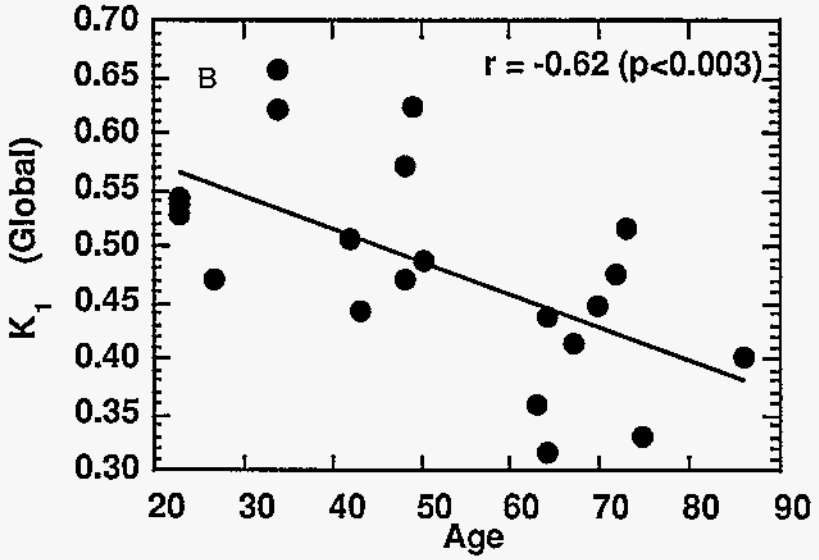

Figure 1. (A) Individual values of MAO B activity (represented by λk_3) versus age ; (B) Individual values of plasma to brain transfer constant (K1) which is related to blood flow versus age.

This study confirms several post-mortem studies reporting increases in brain MAO B with age though the rate of increase is lower than most studies. The whole brain and the cortical regions and the basal ganglia, thalamus, pons and cerebellum showed an average increase of 7.1±1.3 %/decade. The frontal cortex showed a rate of increase of 5.7%/decade which is similar to that reported by Fowler and coworkers [4] but far lower than the increase of 51%/decade reported in a recent post-mortem study [5]. The only brain region where we observe no increase with age is the cingulate gyrus. Though the increases with age is statistically significant, it is noteworthy that there is also a large variability among subjects in the same age range as can be seen from Figure 1A. The factors which account for the difference in magnitude between this PET study and post-mortem studies (and to differences between post-mortem studies) and to the large intersubject variability are not known. However, it is likely that differences in subjects contributes to differences between different studies. In this regard, the difficulty in distinguishing mild dementia from normality in post mortem studies of normal aging have been noted and may have been a factor [2]. Smoking status was not controlled in the post-mortem studies and may have accounted for some of the differences based on the report that smokers have reduced brain MAO B [6]. It would be interesting and important to examine this issue retrospectively.

In summary, we have observed that brain MAO B increases with age in healthy normal subjects who show typical patterns of age related decreases in blood flow. However, the increases we observe are generally smaller than those reported for most post-mortem studies and there is also a relatively large variability in MAO B even within relatively small age ranges in this group of normal, healthy subjects. Thus the extent to which increases in brain MAO B reflects age-related increases in glial cells or whether there are other variables contributing to the results of this PET study and to the range of results reported in the literature requires further investigation.

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