The Investigation of the Active Sites of Monoamine Oxidase (MAO) A and B and the Study of MAO-A Mediated Neurotoxicity Using 4-Substituted Tetrahydropyridines.

by

Sonya L. Palmer

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Approved By:

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Dr. Neal Castagnoli, Jr., Chairman

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Dr. David G. I. Kingston Dr. James M. Tanko

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Dr. Harold Bell Dr. James Wolfe

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ABSTRACT

The mitochondrial membrane bound flavoenzymes monoamine oxidase A and B (MAO-A and MAO-B) catalyze the α-carbon oxidation of a variety of amines including neurotransmitters such as dopamine and serotonin. Although the primary structures of these enzymes have been established from the corresponding gene sequences, relatively little is known regarding the structural features of the active sites which lead to the selectivities observed with various substrates and inhibitors. In spite of many efforts, these enzymes have not been crystallized. In the absence of X-ray structures, the design, synthesis, and evaluation of biological activity remain the only way to assess a view of the active sites, through SAR and QSAR studies. The excellent MAO-A and/or B substrate and inhibitor properties of various 1,4-disubstituted-1,2,3,6-tetrahydropyridine derivatives offer an interesting opportunity to probe the active sites of MAO-A and MAO-B. In an effort to explore the spatial features of the active sites, we have synthesized series of substituted tetrahydropyridines, evaluated their biological activity with purified MAO-A and MAO-B, and carried out a topological analysis of the MAO active sites using molecular modeling. In addition, the results described in this thesis provide evidence that the MAO-A

and MAO-B active sites differ in shape, regions of activity, and areas that tolerate polar interactions.

The role of MAO in neurodegenerative processes such as Parkinson's Disease has been recognized for some time. The structurally unique parkinsonian inducing substrate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is bioactivated to neurotoxic metabolites. The mechanism of neurotoxicity has been studied extensively and it is known that MAO-B catalyzes the conversion of MPTP to the 2,3-dihydro-1-methyl-4-phenylpyridinium species ($MPDP^+$) which undergoes further oxidation to the neurotoxic metabolite 1-methyl-4-phenyl pyridnium (MPP^+). However, the role of MAO-A in mediating a neurotoxic response, has not been fully defined due to the lack of selective MAO-A substrates. In this thesis, we have investigated the neurotoxic potential of several tetrahydropyridines in C57Bl/6 mice and the ability of selective inhibitors to protect against the expression of MAO mediated neurotoxicity.

This thesis is dedicated to my mother Ethelene Brown Palmer and my father the late Leroy Palmer for all their endless love, support and encouragement for all these years.

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