Kinetics of Irreversible Reactions Studied in vitro and in vivo: Monoamine Oxidase Tracers

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Monoamine oxidase (MAO) is an integral protein of outer mitochondrial membranes and occurs in neuronal and non-neuronal cells in the brain and in peripheral organs. It oxidizes amines from both endogenous and exogenous sources thereby influencing the concentration of neurotransmitter amines as well as many xenobiotics and produces hydrogen peroxide as a by-product. MAO also plays an important role in brain development: inhibition of MAO in the developing fetus results in extensive behavioral deficits and MAO knockout mice have distinctive phenotypes. In addition, MAO inhibitor drugs are effective antidepressants and also appear to be beneficial and neuroprotective in Parkinson’s disease.

MAO occurs in two subtypes which are different gene products. MAO A oxidizes norepinephrine and serotonin while MAO B oxidizes phenylethylamine and benzylamine. MAO A is selectively inhibited by clorgyline while MAO B is selectively inhibited by L-deprenyl. Clorgyline and L-deprenyl are mechanism-based irreversible inhibitors (Figure 1). Oxidation of L-deprenyl or clorgyline by MAO produces a highly reactive intermediate within the enzyme substrate complex which irreversibly binds to MAO (referred to as suicide inactivation; Figure 1). Both MAO A and B can be imaged and quantified in the living human brain using positron emission tomography and carbon-11 labeled clorgyline and L-deprenyl and other tracers.

PET studies have been carried out to measure the effects of age, MAO inhibitor drugs, tobacco smoke exposure and other factors on MAO activity in the human brain. In this presentation, we will focus on the following topics directed to developing and refining methods for quantifying MAO A and MAO B availability in the human brain and peripheral organs.

- Kinetic considerations including a discussion of; suicide inactivation; the concept of the rate limiting step; the use of the deuterium isotope effect as a mechanistic tool and to control the rate of binding.
- Demonstration of L-deprenyl specificity and irreversibility in vivo in human brain.
- MAO B measurement in the aging human brain where MAO B is elevated and blood flow is reduced.
- Approaches and limitations for MAO quantification in peripheral organs
- Summary and future directions

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