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Imaging Monoamine Oxidase in the Human Brain

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Positron emission tomography (PET) studies mapping monoamine oxidase in the human brain have been used to measure the turnover rate for MAO B; to determine the minimum effective dose of a new MAO inhibitor drug lazabemide and to document MAO inhibition by cigarette smoke. These studies illustrate the power of PET and radiotracer chemistry to measure normal biochemical processes and to provide information on the effect of drug exposure on specific molecular targets.

INTRODUCTION

Positron emission tomography (PET) is a medical imaging method for measuring the spatial and temporal distribution of positron emitting isotopes in a volume element of tissue. PET is driven by the development of radiotracers labeled with 4 different isotopes shown in Table 1. All of these have very short half-lives and two of them, carbon-11 and fluorine-18 are particularly useful in labeling organic molecules including many drugs. Because the half-lives are short, rapid synthetic methods must be devised. For example, most syntheses with carbon-11 take about 40 minutes and those with fluorine-18 are usually carried out in 2 hours [1]. Because of the short half-lives studies can be performed in humans with low radiation exposure. Since positron decay results in the production of two energetic photons (511 keV) which penetrate the body barrier, the distribution and time-course for these isotopes can be visualized. Labeled compounds whose distribution and kinetics *in vivo* reflect a particular molecular target (receptor, transporter, enzyme), provide the means for visualizing and tracking these processes in the living human body. In this article, we will describe PET studies of the enzyme monoamine oxidase (MAO) in the human brain.

Table 1. Common PET Isotopes

Isotope	Half Life (minutes)
Carbon-11	20.4
Fluorine-18	110
Nitrogen-13	10 min
Oxygen-15	2

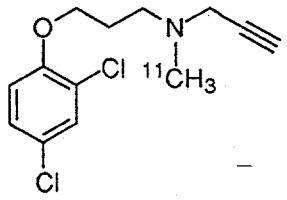
Monoamine Oxidase

Monoamine oxidizes amines including many neurotransmitter amines such as dopamine, norepinephrine and serotonin. MAO catalyzed oxidation results in the inactivation of the neurotransmitter and in the production of hydrogen peroxide (see equation below). It exists in two subtypes, MAO A and MAO B which are different gene products. MAO A and B have different substrate specificities and different inhibitors. MAO A selectively oxidizes norepinephrine and serotonin while MAO B oxidizes phenethylamine,

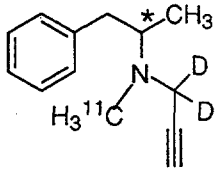
benzylamine and dopamine. MAO B is localized mainly in glial cells and in the serotonergic neurons while MAO A occurs in dopamine and norepinephrine neurons.

$$RCH_2NH_2 + O_2 \xrightarrow{MAO} RCHO + NH_3 + H_2O_2$$

MAO A and B can be imaged in the human brain using PET and the labeled irreversible inhibitors, [^{11}C]clorgyline and [^{11}C]L-deprenyl and deuterium substituted [^{11}C]L-deprenyl respectively [2]. Deuterium substitution of the propargyl group of L-deprenyl improves tracer kinetics and quantitation in brain regions with high enzyme concentration [3]. The mechanism underlying the formation of the PET image of MAO activity involves irreversible covalent attachment of the labeled inhibitor to the enzyme within the enzyme substrate complex. Here we describe PET studies mapping MAO B in the human brain to measure the turnover rate for MAO B in the human brain, to determine the minimum effective dose of a new MAO inhibitor drug, lazabemide and to document MAO inhibition by cigarette smoke.



[^{11}C]clorgyline



[^{11}C]L-deprenyl-D2

MAO B Inhibitor Drugs: The use of labeled L-deprenyl provides the opportunity to study the pharmacodynamics of MAO B inhibitor drugs. Lazabemide was recently introduced as a selective MAO B inhibitor for the treatment of Parkinson's disease [4, 5]. PET with [^{11}C]L-deprenyl was applied to the determination of the minimum effective dose to inhibit >90% MAO B for clinical evaluation in the treatment of Parkinson's disease [6]. Studies were carried out in a group of unmedicated patients with early Parkinson's disease. Each patient received a baseline PET scan with [^{11}C]L-deprenyl and then received either 25 mg, 50 mg or 100 mg of lazabemide twice a day for 1 week. Twelve hours after the last dose of lazabemide, a second PET scan was performed. Comparison of the second scan with the baseline scan showed that the 50 mg dose was sufficient to block >90% of the enzyme whereas the 25 mg dose was inadequate. A third PET scan performed 36 hours after the last dose of lazabemide showed that the inhibition was completely reversible after this short drug free interval. The reversibility of inhibition of lazabemide contrasts sharply with the irreversible inhibition of the enzyme by L-deprenyl. Volunteers were treated with a therapeutic dose of L-deprenyl (10 mg/day) for 1 week. Serial PET studies performed over a 6 week interval after the last dose of L-deprenyl showed that the half-time for recovery of the enzyme was 40 days after drug withdrawal (Figure 1). These PET studies indicate that MAO B inhibition can be maintained at a far lower dose of L-deprenyl than is used [7].

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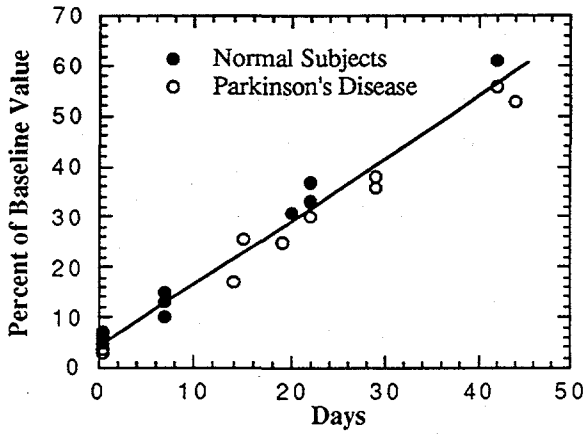

Figure 1. Plot showing the recovery time for MAO B after irreversible inhibition by L-deprenyl. Four PET studies with [^{11}C]L-deprenyl were performed in each subject to track the recovery rate [7].

MAO Inhibition by Tobacco Smoke: During our studies of MAO inhibitor drugs, we found that cigarette smokers had very low brain MAO B while former smokers had normal levels (Figure 2) [8]. Though it was known that substance(s) in tobacco smoke (not nicotine [9]) inhibit platelet MAO [10], this had not previously been demonstrated in the human brain. Newer studies measuring MAO A with [^{11}C]clorgyline showed that smokers also have reduced MAO A [11]. Inhibition is partial, with average reductions of 30% and 40% being observed for MAO A and B respectively. This observation raises intriguing questions as to whether MAO inhibition by smoke may contribute to some of the behavioral and epidemiological features of smoking including the decreased risk of Parkinson's disease in smokers [12] and an increased rate of smoking in depression [13] and in addictions to other substances [14]. The knowledge that there are neuropharmacological effects of smoke apart from those of nicotine may be important in the development of treatments for neurological and psychiatric illnesses as well as for smoking cessation.

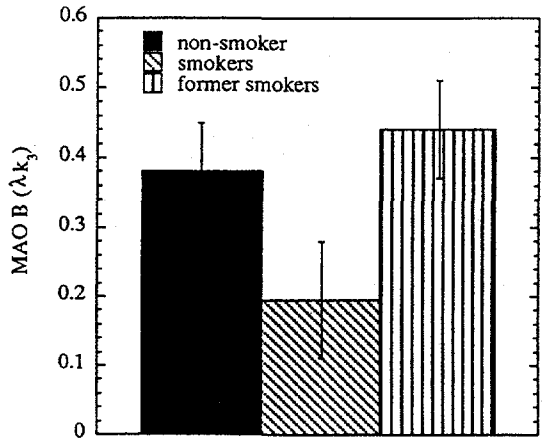

Figure 2. Plot showing MAO B activity in a group of non-smokers, smokers and former smokers.

Summary and Outlook

While PET is technologically complex because the restricted time scale requires that radioisotope production, radiotracer synthesis and PET imaging to be carried out in the same place, the payoff is that compounds labeled with these isotopes can be used to map specific molecular targets and the movement of drugs in the human brain. Providing that appropriate radiotracers are available, one can determine the amount of a drug which gets into the brain, the minimum effective dose, the duration of action or the binding site occupancy required to elicit a particular therapeutic or behavioral effect with a relatively small number of PET studies [15]. And because studies are carried out directly in humans, the relationship of these parameters to behavior and to therapeutic efficacy can be evaluated. The possibilities are enormous and are largely driven by advances in rapid synthesis which synergize with advances in neuropharmacology and advances in PET instrumentation.

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