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Monoamine Oxidase: Radiotracer Development and Human Studies

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1 Introduction

1.1 Discovery

In 1928, Mary Hare isolated a new enzyme which catalyzed the oxidative deamination of tyramine (Hare, 1928). She called it tyramine oxidase and speculated that it "may be protective and present for the purpose of rapid detoxification of excessive amounts of tyramine absorbed from the intestine." Later Blashko and coworkers showed that this same enzyme also oxidized catecholamines (Blashko et al., 1937). To reflect this more general reactivity, Zeller proposed the general name monoamine oxidase (MAO) (Zeller, 1938). In the years that followed its discovery, MAO was further characterized along and its role in the regulation of chemical neurotransmitters, its role as a target in therapeutic drugs and toxic substances and, more recently, its genetics were studied . This chapter will focus on the general aspects of MAO; the development of radiotracers for imaging MAO A and MAO B; PET studies of MAO in the human brain.

1.2 General Features of MAO

Monoamine oxidase (MAO; amine: oxygen oxidoreductase (deaminating) (flavin containing); E. C. 1.4.3.4) 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 (equation 1; Singer, 1995; Richards et al, 1998). It occurs as two subtypes, MAO A and MAO B which have different inhibitor and substrate specificities (Figure 1). MAO A preferentially oxidizes norephinephrine and serotonin and is selectively inhibited by clorgyline (Johnston, 1968) while MAO B preferentially breaks down the trace amine phenethylamine and is selectively inhibited by L-deprenyl (Knoll and Magyar, 1972). Both forms oxidize dopamine, tyramine and octopamine (Youdim and Riederer, 1993). Oxidation is accompanied stoichiometrically by the reduction of oxygen to hydrogen peroxide. The relative ratios of MAO A and B are organ and species specific (see Saura et al, 1994). For example in the human brain, MAO B predominates whereas in the rat brain, MAO A is the predominant subtype. The two subtypes are also compartmentalized in different cell types in the brain with MAO B occurring predominately in glial cells and in serotonergic neurons while MAO A occurs in catecholaminergic neurons as well as in glia cells. It has been

speculated that the compartmentalization of a specific MAO subtypes within the neurons prevents the non-specific neuronal accumulation of neurotransmitters.

(equation 1)

1.3 Genetics

MAO A and B are encoded by separate genes that are closely linked on the X chromosome and share 70% similarity in amino acid sequence (Bach et al., 1988). The loss of both MAO A and MAO B genes has been implicated in the severe mental retardation of some patients with Norrie disease (Collins et al., 1992). Recently a family has been described in which a point mutation in the gene encoding MAO A abolished MAO A activity and is associated with a recognizable behavioral phenotype which includes disturbed regulation of impulsive aggression (Brunner et al., 1993). With the development of molecular genetic techniques for the production of knockout animals, mice missing MAO A or MAO B have been produced and studied. MAO A knockout mice have high circulating levels of serotonin and male animals exhibited a distinct behavioral syndrome characterized by enhanced aggression (Cases et al., 1995). MAO B knockout animals have high levels of phenethylamine, a specific substrate for MAO B and they are resistant to MPTP neurotoxicity (Grimsby et al., 1997). Studies in MAO B knockout mice also suggest that MAO B may regulate normal blood flow distribution (Scremin et al., 1999.) Both MAO A and B knockouts show enhanced reactivity to stress. Transgenic mice overexpressing human MAO B protein have also been described. They express a 4-6-fold higher brain MAO B and a higher rate of dopamine metabolism whereas liver MAO B is equal to that of control littermates (Richards et al, 1998). Transgenic animals have been valuable models for investigating the role of monoamines in psychoses and neurodegeneration and stress-related disorders (Shih et al., 1999).

1.4 Medical Importance

Medical interest in MAO was stimulated in the early 1950's when it was discovered that iproniazide, a drug which was being used to treat tuberculosis, elevated mood in some patients (Selikoff et al., 1952; Crane, 1956). This observation suggested the possibility of treating depression pharmacologically. It was soon learned that iproniazide inhibited MAO (Zeller et al., 1955). This revelation, in part, contributed to the hypothesis that monoamine regulation may be related to mood and led to the development and application of MAO inhibitor drugs in the treatment of depression (Schildkraut, 1965).

Though the MAO inhibitors were effective antidepressants, their use was limited by serious and sometimes lethal side effect which came to be known as the 'cheese effect' (Anderson et al., 1993). This refers to the development of hypertensive crisis in individudals who were taking non-selective, irreversible MAO inhibitor drugs and who also ingested foods (aged cheeses, pickled meats and fish, and red wine) which contain large quantities of the vasoactive amine, tyramine. The breakdown of tyramine requires the presence of MAO in the digestive organs. A number of deaths occurred in the early years of MAO inhibitor therapy before these serious drug-diet interactions were understood and controlled. For this reason, MAO inhibitor drugs were largely supplanted by antidepressant drugs with a more acceptable side effect profile. Because of this initial experience with irreversible MAO inhibitor drugs, MAO's role as a vast and complex mechanism for regulating circulating catecholamines and other endogenous amines as well as dietary amines and drugs as well as its role in regulating blood pressure has come to be appreciated and respected (Kopin, 1993).

Following the initial experience with non-selective, irreversible MAO inhibitors in the treatment of depression, the selective irreversible MAO B inhibitor, L-deprenyl was developed (Knoll and Magyar, 1972). It was used in combination with L-DOPA therapy in Parkinson's disease to inhibit the MAO catalyzed oxidation of dopamine. This combination therapy was reported to have prolonged therapeutic efficacy in patients when compared to L-DOPA alone. Because L-deprenyl has a high selectivity for MAO B, leaving MAO A intact, it does not have the side effects of the non-selective irreversible MAO inhibitors (Birkmayer and Riederer, 1984).

In the early 1980's another chapter in the therapeutic use of L-deprenyl unfolded when it was reported that L-deprenyl could prevent the development of Parkinson's disease in animals treated with 1-methyl-4-phenyl-1,2,3,5-tetrahydropyridine (MPTP) (Heikkila et al, 1984). MPTP was an impurity in a street drug which when ingested caused an initially puzzling outbreak of Parkinson's disease in a number of young people. In a remarkable series of studies, it was discovered that MAO B inhibition prevented MPTP induced neurotoxicity by inhibiting the conversion of MPTP to 1-methyl-4-phenylpyridinium (MPP+) which is toxic to dopamine neurons (Figure 2). This led to speculation that MAO inhibitors may have a neuroprotective effect in Parkinson's disease and to clinical trials showing that L-deprenyl significantly retarded the progression of the disease and the requirement for L-DOPA therapy (Tetrud and Langston, 1989; The Parkinson's Study Group, 1989). The successful use of L-deprenyl monotherapy

stimulated the development of other MAO B inhibitors with enhanced neuroprotective properties and also stimulated discussions as to whether the decreased progression of the disease represented protective or symptomatic effects (Fowler et a., 1996c) and even whether the mechanism involves MAO B inhibition (Ansari et al., 1993).

The structures of some MAO inhibitor drugs are shown in Figure 3.

2 Radiotracer Development

Because the regional and cellular compartmentalization of MAO and its subtypes determines to a large extent the access of specific substrates to each subtype, a knowledge of the distribution of MAO A and B in the brain and the peripheral organs is a crucial element in understanding neurotransmitter regulation and in understanding the MAO inhibitory properties of drugs. Studies in humans are of special value because species variability in MAO subtype distribution limits the relevance of animal measurements. In this section, we describe a number of different approaches have been used to selectively image MAO subtypes. These include the use of reversible, subtype selective radiotracers; compounds which are oxidized by MAO to produce a charged labeled product which is trapped in MAO rich tissues (metabolically trapped radiotracers); compounds which are oxidized by MAO to produce a reactive intermediate which labels MAO by irreversible covalent attachment of the radiotracer to the enzyme (suicide inactivator radiotracers). The functional activity of MAO has also been visualized in vivo in the baboon and human heart by the kinetic behavior and deuterium isotope effects of labeled substrates, 6-[^{18}F]fluorodopamine (Ding et al, 1995) and [^{11}C]phenylephrine (Raffel et al, 1996,1999) (Figure 4). Human PET studies with [^{11}C]phenylephrine (which is a tracer for cardiac vesicular storage sites) showed that C-11 clearance from cardiac storage vesicles in vivo is sensitive to MAO but that the major determinant of clearance of carbon-11 is due primarily to leakage from vesicles. In the case of 6-[^{18}F]fluorodopamine deuterium substitution in the α (position next to the amino group) and β-positions respectively was used to determine whether MAO (which would cleave the α carbon-hydrogen bond) or catecholamine-O-methyltransferase (which would cleave the β carbon-hydrogen bond) contributed to the clearance of fluorine-18 from the heart. Both of these studies illustrate the value of the deuterium isotope effect as a mechanistic tool which essentially isolates the MAO reaction in vivo.

2.1 Reversible, Subtype-Selective Radiotracers

A number of different classes of selective, reversible inhibitors of MAO A and B have been labeled with PET or SPECT radioisotopes and evaluated for their specificity as MAO tracers in vivo. Some of these are shown in Figure 5. Derivatives of the harmine alkaloids have been labeled with C-11 and evaluated in the monkey brain for the assessment for MAO A. [^{11}C]Harmine, [^{11}C]methylharmine, [^{11}C]harmaline, and [^{11}C]brofaromine were compared in rhesus monkey and both [^{11}C]harmine and [^{11}C]methylharmine had favorable binding properties for imaging MAO A (Bergstrom et al., 1997a,b) while [^{11}C]brofaromine, [^{11}C]harmaline and [^{11}C]clorgyline did not show specific binding in this species (Ametamey et al., 1996; Bergstrom et al, 1997b). PET studies of the potency of MAO A inhibitor drugs have been carried out with [^{11}C]harmine (Bergstrom et al, 1997c; see description below).

Befloxatone is an oxazolidinone derivative belonging to a new class of reversible MAO A inhibitors. It is a potent, reversible MAO A inhibitor with activity in animal models of depression (Curet et al., 1996). Interestingly, the structure does not contain a basic amine function. [^{11}C]Befloxatone was synthesized via a cyclization reaction with [^{11}C]phosgene. Studies in the baboon have shown that it rapidly penetrates the brain and shows good characteristics for imaging brain MAO A (Dolle et al., 1999).

A radioiodinated derivative of moclobemide has been developed as a specific radiotracer for MAO A for SPECT. It was shown to have preferential MAO A activity in the brain and mixed MAO A and B activity in peripheral organs possibly due to the production of labeled metabolites with MAO B activity (Rafi et al., 1996).

For SPECT and PET studies of brain MAO B, the pyridine carboxamide, Ro 43-0463 has been labeled with iodine-123 and with fluorine-18 (Beer et al, 1995; Blauenstein et al, 1998). [^{123}I]Ro 43-0463 has appropriate properties for SPECT studies of MAO B in the human brain (see discussion below) whereas the F-18 substituted derivative has brain uptake which is too low for imaging. It was speculated that the low lipophilicity of the F-18 compound limited brain uptake. An oxadiazolone derivative (5-[4-(benzyloxy)phenyl]-3-(2-cyanoethyl)-1,3,4-oxadiazol-2(^{3}H)-one; MD 230254) has been labeled with carbon-11 and evaluated for MAO B imaging in the rat and baboon brain (Bernard et al., 1996). Like befloxatone the structure does not contain a basic amine function and like [^{11}C]befloxatone, it was synthesized from [^{11}C]phosgene. PET

studies in the baboon have shown rapid binding which is reduced by L-deprenyl treatment, consistent with binding to MAO B.

2.2 Metabolic Trapping

Using a different approach, MAO has been imaged using a labeled substrate which is metabolized to produce a charged, labeled product which is intracellularly trapped. This is exemplified by [^{11}C]N,N-dimethylphenethylamine (DMPEA) which is a good substrate for MAO B (Inoue et al, 1985). Images reflect the intracellular trapping of MAO-B generated [^{11}C]-labeled dimethylamine (Figure 6). Mechanistic studies including the demonstration of a deuterium isotope effect and PET studies in the monkey with DMPEA labeled in different positions validated its use as a MAO tracer (Hashimoto et al, 1986; Halldin et al, 1989). PET studies showed that C-11 was trapped in MAO-rich regions in the human brain (Shinotoh et al, 1987).

The same concept has been applied in the heart. [^{13}N]labeled phenethylamine was used to demonstrate the presence of MAO B in the rat heart through the trapping of MAO-generated [^{13}N]ammonium. Deuterium-substituted phenethylamine confirmed that N-13 distribution in the heart represented MAO B activity (Tominaga et al, 1987).

2.3 Suicide Inactivator Approach

The suicide inactivator approach is another form of metabolic trapping. It involves the irreversible covalent binding of the radiotracer to the flavin cofactor of MAO resulting from a highly reactive intermediate which is produced during MAO catalyzed oxidation (Abeles and Maycock, 1976). This approach had a precedent in the biochemical assay of MAO in which suicide inactivators were used to titrate the active centers of MAO in tissue samples (Fowler et al, 1980). The selective irreversible MAO inhibitors clorgyline (Johnston, 1968) and L-deprenyl (Knoll and Magyar, 1972) served as model structures to test this approach for PET imaging of MAO A and MAO B respectively. These compounds were labeled with C-11 for early mechanistic studies in animals (MacGregor et al, 1988; Fowler et al., 1988). Another non-selective suicide inactivator, pargyline was also labeled with carbon-11 and evaluated in animals (Ishiwata et al, 1985). The structures of these labeled compounds are shown in Figure 7. Derivatives of clorgyline, deprenyl and pargyline have also been labeled with iodine-123 and fluorine-18 and evaluated for their potential for PET and SPECT studies (Plenevaux et al., 1990; Mukhergee and Yang, 1999; Lena et al., 1995).

2.3.1 Mechanistic Studies

The kinetic scheme for suicide inactivation involves a branched pathway (Walsh, 1982). The suicide inactivator (S) has a latent reactive functional group. In the case of L-deprenyl or clorgyline, the latent reactive functional group is the propargyl group and this is unmasked within the enzyme substrate complex (E-S) during the catalytic step (Maycock, et al, 1976). The catalytically activated substrate (E-S)* then forms a convalent bond to the flavin cofactor of the enzyme causing irreversible deactivation (E_{inact}; pathway 2) or turnover to regenerate enzyme and form product (P; pathway 1) (scheme 1). This process is commonly referred to as suicide inactivation (or mechanism-based inactivation) because the enzyme catalyzes its own destruction (Abeles and Maycock, 1976).

(scheme 1)

The covalent attachment of the *labeled* suicide inactivator to the enzyme is at the heart of the use of the labeled suicide inactivator approach in PET imaging. Because the interaction of the functionally active enzyme and the labeled suicide inactivator results in a covalent bond (see Figure 8 for the structure of the [^{11}C]L-deprenyl-MAO B adduct), the image of radioactivity distribution after the initial distribution phase has the potential of representing functional enzyme activity. For this approach to be successful, the partition ratio must be small (i.e. the rate of enzyme inactivation (pathway 2) must be greater than the rate of turnover (pathway 1).

Studies in mice demonstrated the feasibility of applying this technique in vivo by showing that carbon-11 labeled clorgyline and L-deprenyl are selective for brain MAO A and MAO B respectively (MacGregor et al, 1985). PET studies with [^{11}C]L-deprenyl in baboons and in humans showed appropriate stereoselectivity (Fowler et al, 1987) and regional distribution, blockade by pharmacological doses of L-deprenyl (Arnett et al, 1987; Fowler et al, 1994).

In addition, the deuterium isotope effect was used to probe the mechanism by which C-11 accumulates in the brain during a PET study with [^{11}C]L-deprenyl. The deuterium isotope effect is based on the fact that a C-D bond is more difficult to cleave than a C-H bond. Thus the substitution of hydrogen by deuterium in a carbon-hydrogen bond can be used to determine whether the rate limiting step in a reaction involves the cleavage of this particular bond. The rate limiting step for MAO oxidation is cleavage of the C-H bond which is α to the amino group (Belleau and Moran, 1963). When [^{11}C]L-deprenyl and deuterium substituted [^{11}C]L-deprenyl

(where deuterium is incorporated in the methylene group of the propargyl group; see Figure 6 for the structure) are compared either in the baboon or in the human brain, there is an isotope effect (Fowler et al, 1988; Fowler et al, 1995) manifested as a reduction in the uptake (Figure 9) and the rate of binding in the brain (Figure 10). This established that MAO catalyzed cleavage of the α carbon-hydrogen bond on the propargyl group is the rate limiting (or a major rate contributing) step in the retention of carbon-11 in brain. This observation forms the basis for the current use of deuterium substituted [^{11}C]L-deprenyl ([^{11}C]L-deprenyl-D2) in human studies to increase tracer sensitivity in regions of high MAO B concentration (Fowler et al, 1995).

Deuterium substitution has also been used to demonstrate that the binding of [^{11}C]clorgyline in the human brain represents MAO A activity (Fowler et al., 2000b). In addition, pretreatment with a low dose of tranylcypromine (a non-selective irreversible MAO inhibitor; 10 mg/day for 3 days) reduced [^{11}C]clorgyline binding by an average of 58% (Figure 11) demonstrating that [^{11}C]clorgyline binds to MAO A in the human brain (Fowler et al. 1996b). Note that this contrasts with lack of specific binding of [^{11}C]clorgyline in rhesus monkey (Bergstrom et al., 1997b) illustrating an unusual case where the binding of a specific radiotracer differs markedly for the rhesus monkey and human.

2.3.2 Quantitation of Functional MAO Activity in the Human Brain

A three-compartment kinetic model has been developed and applied to the quantitation of the binding of the [^{11}C]suicide inactivators of MAO A and B in the baboon and human brain. The model requires the measurement of the time course of radioactivity in the brain and in the arterial plasma. Its application allows the calculation of the model term K_1, the plasma to brain transfer constant which is related to blood flow, and λk_3 which is proportional to the concentration of catalytically active MAO molecules.

The kinetic scheme that incorporates the reversible transfer of labeled substrate between blood and brain and all of the major steps in suicide inhibition including normal enzyme turnover as well as suicide inactivation is given below (Fowler et al, 1988; Walsh, 1982). In this model S_p is the concentration of labeled L-deprenyl in arterial plasma, S_b is the concentration of labeled tracer in brain that has not reacted with the enzyme, E is the concentration of free (unbound) enzyme, E-S is the enzyme-substrate complex, E_{inact} is the inactivated enzyme, [E-S]* is the catalytically activated intermediate, P is the product of enzyme reaction, K_1 is the transfer constant describing the transport of substrate from plasma to brain, k_2 is the transfer

constant describing the transport of substrate from brain to plasma, k_3 is is the bimolecular rate constant (concentration^{-1} x min^{-1} of the enzyme-substrate complex), k_4 is the first order constant for dissociation of the enzyme substrate complex (min^{-1}), k_5 is the first order constant for the formation of intermediate [E-S]* (min^{-1}), k_6 is the constant for formation of the enzyme and product (min^{-1}). and k_7 is the formation of inactivated enzyme (min^{-1}) (scheme 2).

(scheme 2)

Since PET measures the total radioactivity in a given region of interest and cannot measure the concentrations of the intermediate species, all of the species in the box labeled PET Region of Interest are indistinguishable to the tomograph. As a result, it is not possible to uniquely determine all constants and therefore a simpler model shown below is used (scheme 3) where S_{tr} is the concentration of labeled L-deprenyl bound to enzyme and k'_3 is a kinetic term related to the processes involved in the trapping of carbon-11 in tissue.

(scheme 3)

The differential equations corresponding to this model are given by

$$dS_b / dt = K_1 S_p(t) - k_2 S_b - (k'_3 E) S_b$$
$$dS_{tr} / dt = (k'_3 E) S_b$$

The model equations are solved using for the input function the arterial plasma radioactivity corrected for the fraction of [^{11}C]radiotracer at different time points and model constants were optimized to obtain the best fit to the data. The following assumptions are made:

(1) The specific activity of labeled radiotracer is sufficiently high that the free enzyme concentration does not change during the course of the experiment and that the enzyme concentration is included in $k'_3 E$. In the case of [^{11}C]L-deprenyl used in studies of drug efficacy (Fowler et al, 1993), the maximum injected dose was 44 micrograms. Using the uptake of 0.0076%/g in the basal ganglia and a MAO B concentration of 2 pmol/mg protein (200 nM) (Oreland, 1991), the concentration of [^{11}C]L-deprenyl (bound to enzyme) would be 18 nM well below the MAO B concentration as well as the Km for L-deprenyl (325 nM (Robinson, 1985). Under these conditions $k'_3 E$ is constant and proportional to the free enzyme concentration. Depending on which step in the process of inactivation is rate limiting, $k'_3 E$ in the 3

compartment model can be related to different rate constants in the multi-step process but should always be proportional to the free enzyme concentration (Fowler et al, 1988). On this basis, the comparison of values of $k'_3 E$ for an individual at baseline, to $k'_3 E$ for the same individual during drug treatment and washout should permit the assessment of relative changes in enzyme concentration.

(2) The kinetic term, k_4, which represents loss of radioactivity from the [^{11}C]L-deprenyl-MAO B complex is set to zero, since it is known that the turnover time of MAO B after inactivation by L-deprenyl is on the order of weeks in baboons (Arnett et al, 1987) and humans (Fowler et al, 1994).

(3) Although the three model parameters (K_1, k_2 and $k'_3 E$) of Scheme 3 can be determined, reproducibility is improved if the term compared is $\lambda k'_3 E$ (where $\lambda = K_1 / k_2$) rather than $k'_3 E$. For simplicity we will use λk_3 rather than $\lambda k'_3 E$ to refer to Scheme 3. This is due to the fact that k_2 and $k'_3 E$ are highly correlated. This is especially evident in regions of high enzyme concentration that may have optimum values of both terms that are lower than expected. This can be overcome by either fixing λ thus reducing the number of model parameters to be optimized or by determining all three and using the composite parameter λk_3 as the measure of enzyme concentration. Even though the transport constants K_1 and k_2 depend upon blood flow, their ratio does not (Logan et al, 1991).

A problem encountered with irreversible tracers is that if the trapping rate is too high compared to the rate of efflux (k_2), the observed uptake is related to blood flow alone and contains no information about enzyme concentration. This is the "flow limited" situation. This is a difficulty encountered with [^{11}C]L-deprenyl when MAO B concentration is high and blood flow is low as would be encountered in neurodegenerative disorders and aging. Deuterium substitution in [^{11}C]L-deprenyl decreases the trapping rate (λk_3) but not the delivery rate (K_1) and therefore increases the sensitivity of the uptake to MAO B (Fowler et al., 1995). Under these conditions, the three-compartment model provides a better measure of MAO concentration ((Fowler et al., 1988, 1993; Lammertsma et al., 1991).

Human PET studies have shown that repeated measures of [^{11}C]L-deprenyl-D2 binding in the human brain are reproducible based on comparison of $\lambda k'_3 E$ (Logan et al., 2000). $\lambda k'_3 E$ can also be derived from a linear form of the model equations making use of the graphical

analysis for irreversible systems (Patlak et al., 1983) which quantitates the uptake of L-deprenyl in terms of the influx constant, K_i. However, K_i is a function of blood flow and therefore it is necessary to also determine K_1 and λk_3 can be derived from K_i and K_1. The linear method is rapid but can produce biased estimates due to correlated noise. However using ROI analysis with low noise, results from both the linear and nonlinear methods were shown to be in good agreement (Logan et al., 2000). The graphical analysis for irreversible systems (Patlak et al, 1983) is applicable to L-deprenyl but the influx constant, K_i is a function of blood flow, whereas $\lambda k'_3 E$ is not.

3 Human Studies

The development of radiotracers for visualizing MAO quantiatively in the human body has been driven by many factors including speculation that MAO may play a pathophysiological role in aging and neurodegeneration; its role as a target for therapeutic drugs and neurotoxic substances; its role in the detoxification of xenobiotic amines; its proposed role as a biological marker in certain diseases and behaviors. Some of these studies are described below.

3.1 MAO B in the Normal Human Brain: Effects of Age

Many neuronal cells and their associated neurotransmitters and enzymes show age-related losses (Carlson, 1987; Palmer and DeKosky, 1993. However, MAO B is an exception. Studies in the human brain post-mortem report that MAO B increases with age (Fowler et al, 1980; Galva et al, 1995; Robinson et al, 1971) and in neurodegenerative disease (Saura et al, 1994). This is consistent with the compartmentalization of MAO B within glial cells (Westlund et al, 1988) and with reports that the number of glial cells increases with age in the normal human brain (Terry et al, 1987) and in neurodegenerative disease (Strolin-Benedetti and Dostert, 1989; Saura et al, 1994). It has been proposed that increases in brain MAO B with aging increases oxidative stress and that this may play a role in the vulnerability of the brain dopamine system to age-related degeneration (Cohen and Kesler, 1999).

Brain MAO B has been measured in a group of normal healthy subjects (n=21; age range 23-86; 9 females and 12 males; non-smokers) using deuterium substituted [^{11}C]L-deprenyl ([^{11}C]L-deprenyl-D2) (Fowler et al, 1995). MAO B concentration using the model term λk_3 (Fowler et al, 1997). The regional distribution of MAO B was highest in the basal ganglia and the thalamus with intermediate levels in the frontal cortex and the cingulate gyrus and lowest

levels in the parietal and temporal cortices and the cerebellum. MAO B increased significantly with age ($p<0.004$) in all brain regions examined except the cingulate gyrus. The same patterns remained when the correlation analysis was performed separately for men and for women. 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 over the age range 23-86 years. The frontal cortex showed an average rate of increase of 5.7%/decade. The correlation coefficient between age and λk_3, the model parameter for MAO B for the frontal cortex corresponded to 0.66, a value similar to those reported in post-mortem studies (range 0.45-0.71) . This indicates that while age is a factor contributing to the variability among subjects, it is not the only one.

[^{11}C]L-deprenyl-D2 has tracer characteristics which allow the calculation of a plasma to brain transfer constant (K_1) a model term which is related to brain blood flow. In contrast to λk_3 (MAO B) which increased with age, K_1 decreased with age in all regions except for the pons and cerebellum. The highest correlations were in the frontal, temporal and parietal cortices. The correlation coefficients for λk_3 and for K_1 are shown in Table 1.

The use of the deuterium substituted tracer was essential in this study because the rapid rate of binding of [^{11}C]L-deprenyl leads to an underestimation of MAO B levels when enzyme concentration is high as is the case in aging. In this case, the rate of delivery of the tracer (K_1) limits the uptake and thus blood flow cannot be well resolved from MAO activity, This is exacerbated in studies of aging where brain blood flow is expected to decrease with age while MAO B activity increases. With [^{11}C]L-deprenyl-D2, the reduced rate of cleavage of the C-D bond results in improved sensitivity (Fowler et al, 1995).

3.2 MAO B Imaging in Gliosis

The known elevation of MAO B in neurodegenerative diseases and brain injury provides an opportunity to explore the use of MAO B tracers as *positive* markers for brain injury and degeneration. Neurodegenerative processes and brain injury are frequently accompanied by gliosis. Because MAO B is located in glial cells, uptake would be high where the concentration of glial cells is high. In principal this could provide a positive complement for tracers like FDG whose uptake is normally decreased in degenerative processes. For example, it is known from PET imaging studies with [^{11}C]L-deprenyl-D2 that MAO B is elevated in the hypometabolic regions in patients with temporal lobe epilepsy where analysis of resected tissue confirmed gliosis (Kumlien, 1992, 1995; Bergstrom et al., 1998). A similar observation (i.e. increased

radiotracer uptake in the ipsilateral mesial temporal lobe) was made with SPECT using [^{123}I]Ro 43-0463 (Buck et al, 1998). A recent study of head trauma patients did not find an inverse relationship between MAO B and glucose metabolism indicating that prospective studies are needed to determine the pathophysiology of hypometabolic lesions in head trauma (Fowler et al., 1999a).

Reports that MAO B is elevated Alzheimer's brain post-mortem (Adolfsson et al., 1980; Reinikainen et al., 1988; Saura et al., 1994), the observation that MAO B is expressed in astrocytes of senile plaques (Nakamura et al., 1990) and an abstract describing increased levels of [^{11}C]L-deprenyl binding in the brains of Alzheimer's patents (Bench et al., 1993) suggests a role for MAO B imaging in studies of the development and progression of Alzheimer's disease.

3.3 MAO B Inhibitor Drugs

The use of MAO inhibitors in the treatment of disease is grounded both in their ability to increase the bioavailability of neurotransmitters and to reduce oxidative stress. Major indications in the development of new MAO inhibitor drugs are in the treatment of neurodegenerative disorders and also the treatment of depression. The newer reversible MAO A inhibitors are of particular interest because of reduced side-effect liability vis a vis drug-diet or drug-drug interactions (Caldecott-Hazard and Schneider, 1992). Imaging studies in humans have focussed on determining the efficacy and minimum effective doses of MAO inhibitor drugs and duration of drug action.

3.3.1 Lazabemide (Ro19 6327): Reports that L-deprenyl reduces the rate of progression of Parkinson's disease stimulated the development of other MAO B inhibitor drugs in order to enhance the neuroprotective effects. One of these drugs was lazabemide (Ro19 6327), an irreversible and highly selective MAO B inhibitor (DaPrada et al, 1988). The development of [^{11}C]L-deprenyl provided the opportunity to determine the efficacy of lazabemide to inhibit MAO B directly in the human brain. Studies were designed to determine minimum effective doses to inhibit >90% of brain MAO B for clinical trials and to determine duration of action (Bench et al., 1991; Fowler et al., 1993). One of the studies was carried out in a group of six 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. This study helped to establish the dose and frequency with which lazabemide would be given in clinical trials. Clinical studies with lazabemide indicate that the pattern of benefits in patients with Parkinson's disease is similar to that of L-deprenyl (Parkinson's Study Group, 1996).

3.3.2. L-Deprenyl (Selegiline): L-Deprenyl has an intriguing combination of catecholaminergic and neuroprotective effects and a relatively benign side effect profile (Koller and Giron, 1990). This is the basis for its use in the treatment of Parkinson's disease and the investigation of its use for the treatment of other neurological and psychiatric disorders including Alzheimer's disease (Sano et al., 1997), schizophrenia (Bodkin et al., 1996), cocaine addiction (Bartzokis et al., 1999) and smoking addiction (Brauer et al., 2000). PET has been used to study L-deprenyl pharmacodynamics including the duration of MAO B inhibition and its specificity for MAO B vs MAO A.

In contrast to the reversible MAO B inhibitor lazabemide, PET studies have shown that MAO B inhibition persists long after the last dose of L-deprenyl. In this study, four elderly normal subjects and 4 unmedicated patients with a diagnosis of idiopathic Parkinson's disease received a baseline PET scan with [^{11}C]L-deprenyl and were the treated with a therapeutic dose of L-deprenyl (10 mg/day) for 1 week. A total of four PET scans (including the baseline) was performed on each subject over a six week interval following the last dose of L-deprenyl. Timing for the four scans was as follows: the first (baseline) was carried out before L-deprenyl; the second at 12 hours after the last dose; the third at 1-2 weeks and the fourth at 3-6 weeks after the last dose of L-deprenyl. Model equations were solved using time-activity data from different brain regions and the input function from the arterial plasma corrected for the presence of labeled metabolites. The half-time for recovery of the enzyme was 40 days after drug withdrawal (Figure 12) demonstrating that MAO B inhibition can be maintained at a far lower dose of L-deprenyl than is currently used (Fowler at al, 1994). In addition to providing information on the duration of MAO B inhibition after L-deprenyl is withdrawn, this study also demonstrates the feabilility of measuring the rate of enzyme protein turnover. Since MAO B is an integral protein of the outer mitochondrial membrane, its recovery after irreversible inactivation requires the removal of inactivated MAO B from the membrane, the synthesis of MAO B protein in cytosolic

ribosomes (a process encoded on the nuclear gene), and insertion of the protein into the outer mitochondrial membrane (Zhuang et al, 1988).

One key issue in characterizing the molecular mechanisms contributing to the therapeutic effects of L-deprenyl is to distinguish MAO B inhibition from other mechanisms. The slow recovery of brain MAO B clearly opens up the possibility that the symptomatic effects of L-deprenyl could persist long after the last dose of the drug. Thus with a half-time of 40 days for the recovery of MAO B, a drug-free interval of several months would be required for brain MAO B to reach >90% of baseline values. This is an important issue in L-deprenyl therapy. The assessment of symptoms after a long term drug-free interval would assure the absence of long term symptomatic effects. This would reduce ambiguity in distinguishing symptomatic from neuroprotective effects (Fowler et al, 1996c) though ethical considerations may preclude such a lengthy drug-free interval.

Though L-Deprenyl is a selective MAO B inhibitor (Knoll and Magyar, 1972), its pharmacology is complex and a number of other mechanisms including partial MAO A inhibition have been proposed to account for its therapeutic effects (Gerlach et al, 1992; Lamensdorf et al., 1996; Riederer and Youdim, 1986). The effect of L-deprenyl treatment on brain MAO A was investigated in six normal volunteers who received L-deprenyl (10 mg/day) for 1 week. Each subject had two PET scans with the MAO A radiotracer [^{11}C]clorgyline, one at baseline and one following L-deprenyl therapy. A 3-compartment model was used to compare the plasma-to-brain transfer constant, K_1 and λk_3 before and after treatment. L-Deprenyl treatment did not affect either brain MAO A activity or K_1 for any of the 12 brain regions examined (Fowler et al., 2000c; Figure 13). This confirms that L-deprenyl is selective for MAO B, though it is possible that selectivity may not be maintained with longer administration.

3.3.3 MAO A Inhibitors (esuprone and moclobemide): There is evidence that antidepressant properties of the MAO inhibitors reside in the inhibition of MAO A and not MAO B. For this reason reversible inhibitors of MAO A which would maintain the therapeutic properties and reduce the potential for interactions with tyramine (Caldecott-Hazard and Schneider, 1992) have been an attractive target in drug development.

Esuprone (Figure 3) is a potent subtype-selective reversible inhibitor of MAO A (IC_{50}: 8.4 nM). PET and the MAO A radiotracer [^{11}C]harmine was used to determine whether or not the new reversible MAO A inhibitor drug esuprone binds substantially to MAO A in the human

brain (Bergstrom et al., 1997a). Volunteers were given daily doses of esuprone (800 mg) or moclobemide (300 mg twice a day) or placebo tablets for a week. PET studies with [^{11}C]harmine were performed at baseline (before drug/placebo) and on day 7 after the previous days treatment for esuprone and 11 hours after the previous day's treatment with moclobemide. Both esuprone and moclobemide reduced [^{11}C]harmine binding to a similar extent relative to baseline. In the placebo group no change was observed. This study showed that esuprone had similar efficacy to inhibit MAO A as moclobemide. This study and similar studies of other drugs illustrate the possibility of obtaining information on drug efficacy directly in the brain rather than to rely on traditional pharmacokinetic measurements.

3.4 MAO and *Ginkgo biloba*

Extracts of *Ginkgo biloba* have been reported to reduce the symptoms of mental decline and this property is generally attributed to the principal active chemical components, flavenoids and the terpenoids, ginkgolides and bilobalide (Curtis-Prior et al, 1999 for review). These CNS effects of *Ginkgo biloba* have stimulated numerous investigations on the mechanisms which may contribute to this property. One hypothesis is that extracts of *Ginkgo biloba* inhibit MAO A and B based on studies in rat brain *in vitro* (White et a, 1996). In order to investigate whether extracts of *Ginkgo* inhibit MAO A and B in the human brain, ten normal healthy volunteers were treated for 1 month with 120 mg/day of the *Ginkgo biloba* extract EGb 761 (Fowler et al., 2000a). [^{11}C]Clorgyline and [^{11}C]L-deprenyl-D2 were used to measure MAO A and B respectively at baseline (before Ginkgo) and after the 1 month treatment period. A three-compartment model was used to calculate the plasma to brain transfer constant K_1 which is related to blood flow and λk_3 which is proportional to the concentration of catalytically active MAO molecules. *Ginkgo biloba* administration did not produce significant changes in brain MAO A or MAO B. This study suggests that mechanisms other than MAO inhibition need to be considered as mediating some of its CNS effects. The lack of MAO inhibitory potency of *Ginkgo biloba* has been recently demonstrated in other systems (Porsolt et al, 2000).

3.5 MAO and Tobacco Smoke

It has been known for many years that platelet MAO is significantly lower in smokers (Oreland et al., 1981). However, MAO levels increase in smokers who quit indicating that low MAO B is a pharmacological effects of the smoke rather than a biological characteristic of smokers (Norman et al, 1987). Similar to the findings of low platelet MAO in smokers, PET

studies of normal volunteers revealed that cigarette smokers had very low brain MAO B while former smokers have normal levels (Fowler et al, 1996a). Furthermore, PET studies measuring MAO A with [^{11}C]clorgyline showed that smokers also have reduced MAO A (Fowler et al, 1996b). Inhibition is partial, with average reductions of 30% and 40% being observed for MAO A and B respectively (Figure 14). 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 (Morens et al, 1995) and an increased rate of smoking in depression (Glassman et al, 1990) and in addictions to other substances (Henningfield et al, 1990) and a general prevalence of smoking in psychiatric ilnesses (Hughes et al, 1986). Reductions in MAO A and B, in principle, could spare neurotransmitters from oxidation and reduce the production of hydrogen peroxide, a byproduct of MAO catalyzed oxidation. MAO inhibition may act synergistically with the dopamine-releasing properties of drugs of abuse by protecting dopamine from metabolism.

Interestingly, nicotine does not inhibit platelet MAO when it is present in the concentrations normally achieved during smoking (Oreland et al, 1981) nor does it inhibit MAO B in the living baboon when administered intravenously (Fowler et al, 1998). Recently the fractionation of extracts from flue-cured tobacco leaves led to the isolation of a competitive inhibitor of human MAO-A (K(i) = 3 μM) and MAO-B (K(i) = 6 μM), the structure of which could be assigned as 2,3,6-trimethyl-benzoquinone, by classical spectroscopic analysis and confirmed by synthesis (Khalil et al, 2000). This information may help to provide insights into some aspects of the pharmacology and toxicology of tobacco products.

While tobacco smokers have an average of 40% lower values of brain MAO B than non-smokers and former smokers, the degree of MAO B inhibition is quite variable between subjects, ranging between 17 and 67%. The variability in the level of inhibition between the smokers was not accounted for by the smoking duration (average 24 ± 13.5 years) or the frequency (average 1±0.27 packs/day). Because the time interval between the PET MAO B measurements and the last cigarette varied between subjects (range 1.7-12 hours), it was of interest to assess if this time interval contributed to the variability in MAO B. A study was undertaken to determine whether MAO B activity recovered measurably after an overnight smoke free interval (Fowler et al, 2000c). Brain MAO B was measured using PET and [^{11}C]L-deprenyl-D2 in six smokers who were scanned twice once at 11.3 hours (baseline) after last cigarette and once at 10 minutes after

smoking. Brain MAO B levels as measured by the model term λk_3 levels did not differ between baseline and after smoking.

Another aspect of the pharmacodynamic relationship between tobacco smoke exposure and MAO inhibition relates to whether MAO inhibition can be detected after a *single* cigarette. For this purpose brain MAO B was measured in a group of 8 non-smokers at baseline and immediately after smoking a single cigarette using [^{11}C]L-deprenyl-D2 and PET. Eight normal healthy non-smokers (35±11 years) received two PET studies 2 hours apart with [^{11}C]L-deprenyl-D2, one at baseline and the second 5-10 minutes after the subject has smoked a single cigarette (Fowler et al., 1999b). Plasma nicotine and expired carbon monoxide (CO) were measured prior to smoking and 10 minutes after smoking completion as an index of tobacco smoke exposure. A 3-compartment model was used to calculate λk_3, a model term proportional to MAO B and K_1, the plasma-to-brain transfer constant which is related to brain blood flow. The average λk_3 and K_1 for 11 different brain regions did not differ significantly between baseline and smoking. These results indicate that the reduction in MAO B in smokers occurs gradually and requires chronic tobacco smoke exposure.

The observation that smokers have reduced brain MAO A and B raises the need to investigate whether MAO B inhibition may account for some of the behavioral and epidemiological features of smoking (Hughes et al., 1986). It also reinforces the importance of reporting smoking status in clinical studies and the need to reevaluate reports that low platelet MAO B is a biological marker in clinical populations where the rate of smoking is high such as schizophrenia (Lidberg et al., 1985). In fact, normal platelet MAO was recently reported in non-smoking patients with schizophrenia (Simpson et al., 1999).

Smoking remains a major public health problem. Yet advances in treating smoking addiction hinge on characterizing both the neuropharmacological effects of tobacco smoke and factors accounting for individual variability in smoking toxicity. Along this line recent studies reporting the use of the reversible MAO A inhibitor moclobemide (Berlin et al,1995a,b) and the combination of nicotine and L-deprenyl (Brauer et al, 2000) as smoking cessation treatments is an important step based on the knowledge that the effects of tobacco smoke go beyond the effects of nicotine.

4 Summary and Outlook

PET is uniquely capable of providing information on biochemical transformations in the living human body. Although most of the studies of MAO have focussed on measurements in the brain, the role of peripheral MAO as a phase 1 enzyme for the metabolism of drugs and xenobiotics is gaining attention (Strolin Benedetti and Tipton, 1998; Castagnoli et al., 1997). MAO is well suited for this role because its concentration in organs such as kidneys, liver and digestive organs is high sometimes exceeding that in the brain. Knowledge of the distribution of the MAO subtypes within different organs and different cells is important in determining which substrates (and which drugs and xenobiotics) have access to which MAO subtypes. The highly variable subtype distribution with different species makes human studies even more important. In addition, the deleterious side effects of combining MAO inhibitors with other drugs and with foodstuffs makes it important to know the MAO inhibitory potency of different drugs both in the brain and in peripheral organs (Ulus et al., 2000). Clearly PET can play a role in answering these questions, in drug research and development and in discovering some of the factors which contribute to the highly variable MAO levels in different individuals.

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Figure Legends

Figure 1. Structures of MAO A and MAO B and MAO A and B substrates.

Figure 2. MAO catalyzed conversion of MPTP to MPP+.

Figure 3. Structures of some MAO inhibitor drugs. The letter in parenthesis indicates subtype specificity.

Figure 4. Structures of 6-[^{18}F]fluorodopamine and [^{11}C]phenylephrine and deuterium substituted derivatives.

Figure 5. Structures of reversibly binding radiotracers for MAO A and B for PET and SPECT studies.

Figure 6. Carbon-11 and nitrogen-13 labeled substrates for MAO B which produce labeled metabolites which are intracellularly trapped as a result of MAO B catalyzed oxidation.

Figure 7. Carbon-11 labeled suicide inactivators of MAO A ([^{11}C]clorgyline) and MAO B ([^{11}C]L-deprenyl and [^{11}C]L-deprenyl-D2) and the non-selective MAO A and B inhibitor [^{11}C]pargyline. The arrows indicate the bonds which are cleaved by MAO in the rate limiting step of catalysis.

Figure 8. Possible structure of the adduct between [^{11}C]L-deprenyl and MAO B (based on Maycock et al., 1976).

Figure 9. Comparison of the uptake (% injected dose/cc; mean ± sdm) of [^{11}C]L-deprenyl (squares) and [^{11}C]L-deprenyl-D2 (circles) in different regions of the human brain (n=5) (Fowler et al., 1995).

Figure 10. Comparison of the time-activity curves for one subject for [^{11}C]L-deprenyl (squares) and [^{11}C]L-deprenyl-D2 (circles) in the human thalamus (A) and cerebellum (B) (Fowler et al., 1995).

Figure 11. Comparison of MAO A (as represented by the model term λk_3) for four healthy volunteers at baseline and after the non-selective MAO inhibitor drug tranylcypromine (10 mg/day) for 3 days (Fowler et al., 1996b).

Figure 12. Recovery of brain MAO B activity in elderly normal subjects and in patients with Parkinson's disease after withdrawal from L-deprenyl, which had been given for 1 week (10 mg/day). PET measures of MAO B using [^{11}C]L-deprenyl at various times after the last dose of L-deprenyl allowed the calculation of the half-time for MAO B synthesis in the brain (about 40 days) (Fowler et al., 1994).

Figure 13. Comparison of MAO A (as measured by [^{11}C]clorgyline and as represented by the model term λk_3; mean ±sdm) in different brain regions for six healthy volunteers at baseline and after treatment with the MAO B selective drug L-deprenyl (10 mg/day) for 3 days. There were no significant differences indicating that selectivity for MAO B is maintained for a 1 week treatment period (Fowler et al., 2000c).

Figure 14. Bar graphs comparing K_1 (plasma to brain transfer constant) and λk_3 (MAO A) (panel A) and MAO B (panel B) in non-smokers and in smokers. Note that there were no significant differences in K_1 while MAO A and B were significantly reduced in the smokers brain (Fowler et al., 1996a,b).

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$$RCH_2NH_2 + O_2 + H_2O \xrightarrow{MAO} RCHO + NH_3 + H_2O_2$$

eq 1

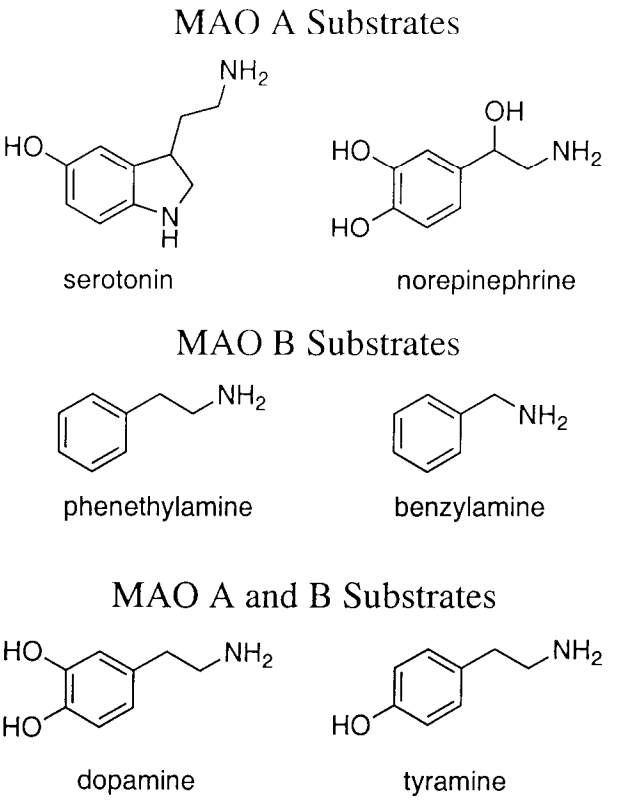


Figure 1. Structures of MAO A and MAO B and MAO A and B substrates.

Fig 1

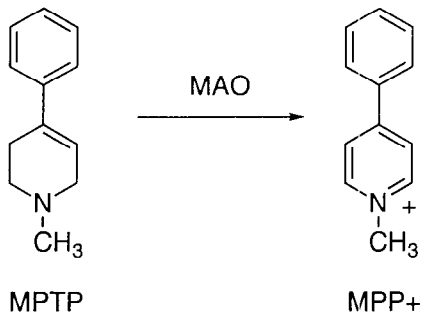


Figure 2. MAO catalyzed conversion of MPTP to MPP+.

Fig 2

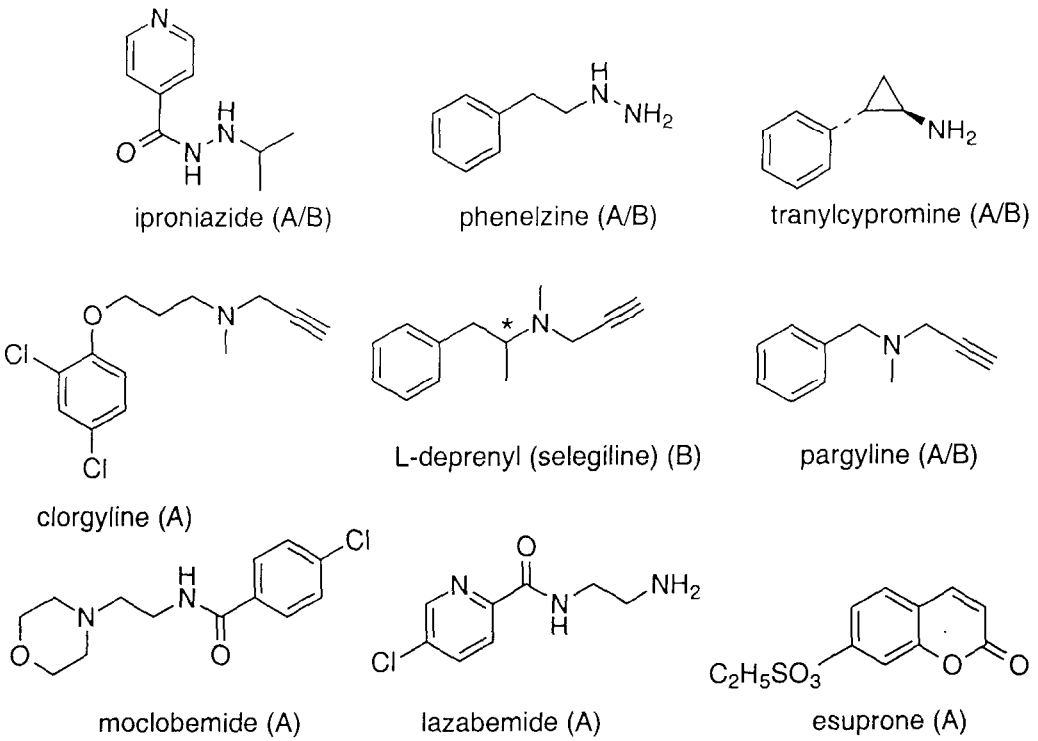
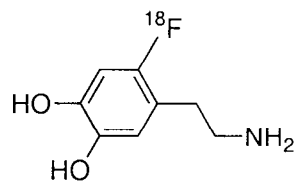
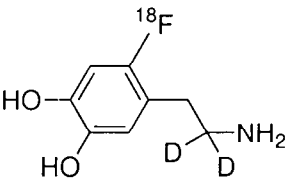


Figure 3. Structures of some MAO inhibitor drugs. The letter in parenthesis indicates subtype specificity.

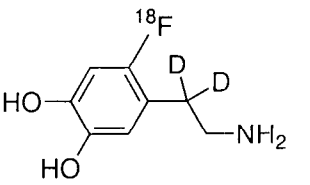
Fig. 3



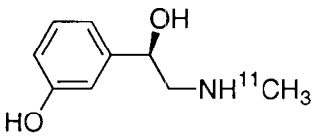
6-[^{18}F]fluorodopamine



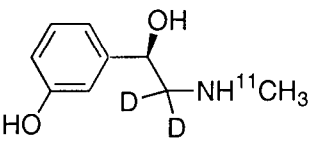
6-[^{18}F]fluorodopamine-α,α,-D2



6-[^{18}F]fluorodopamine-β,β-D2



[^{11}C]phenylephrine



[^{11}C]phenylephrine-α,α-D2

Figure 4. Structures of 6-[^{18}F]fluorodopamine and [^{11}C]phenylephrine and deuterium substituted derivatives.

Fig 4

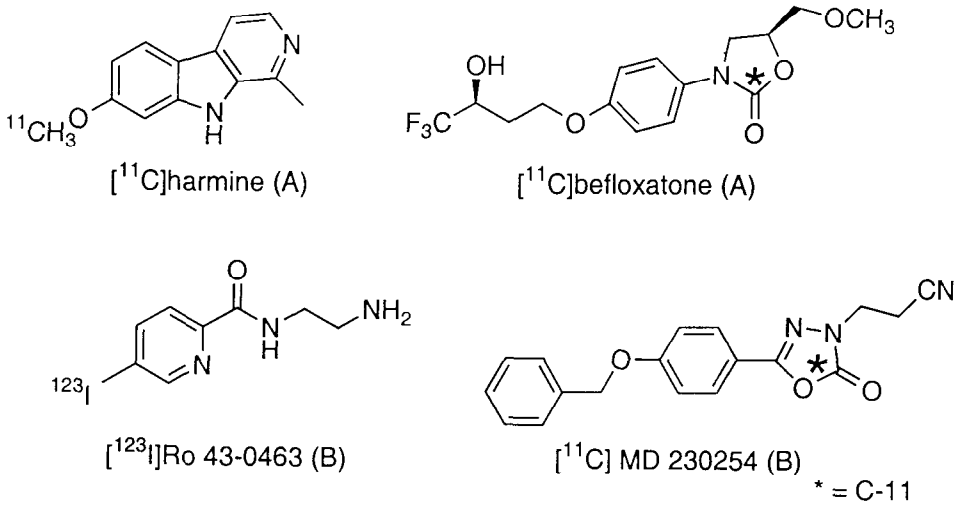


Figure 5. Structures of reversibly binding radiotracers for MAO A and B for PET and SPECT studies.

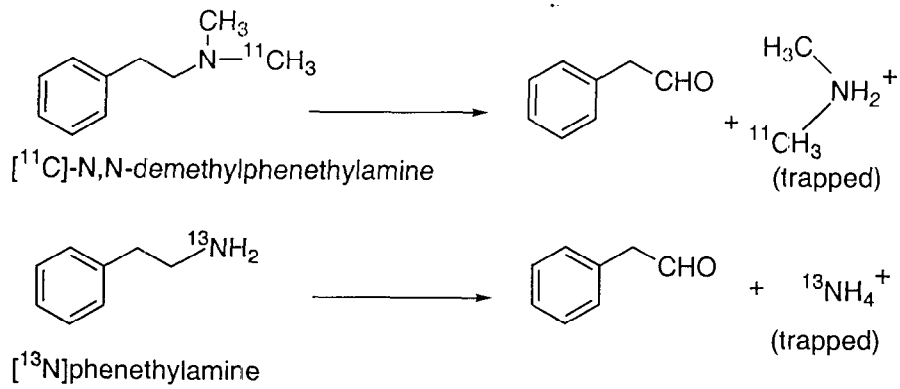
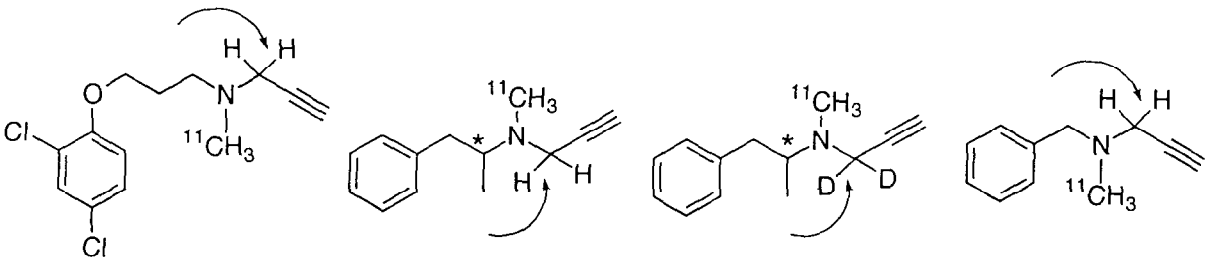


Figure 6. Carbon-11 and nitrogen-13 labeled substrates for MAO B which produce labeled metabolites which are intracellularly trapped as a result of MAO B catalyzed oxidation.



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

Figure 7. Carbon-11 labeled suicide inactivators of MAO A ([^{11}C]clorgyline) and MAO B ([^{11}C]L-deprenyl and [^{11}C]L-deprenyl-D2) and the non-selective MAO A and B inhibitor [^{11}C]pargyline. The arrows indicate the bonds which are cleaved by MAO in the rate limiting step of catalysis.

Fig 7

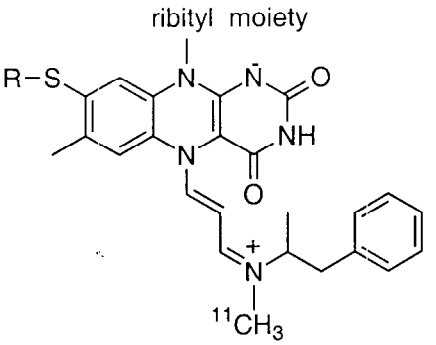
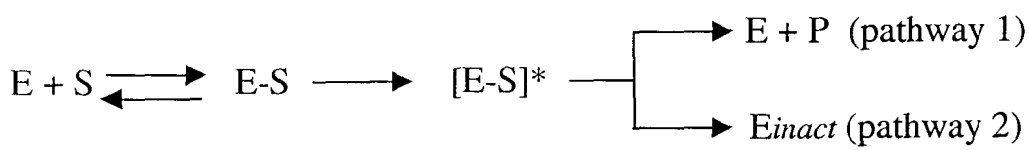


Figure 8. Possible structure of the adduct between [^{11}C]L-deprenyl and MAO B (based on Maycock et al., 1976).

Fig 8



Scheme 1

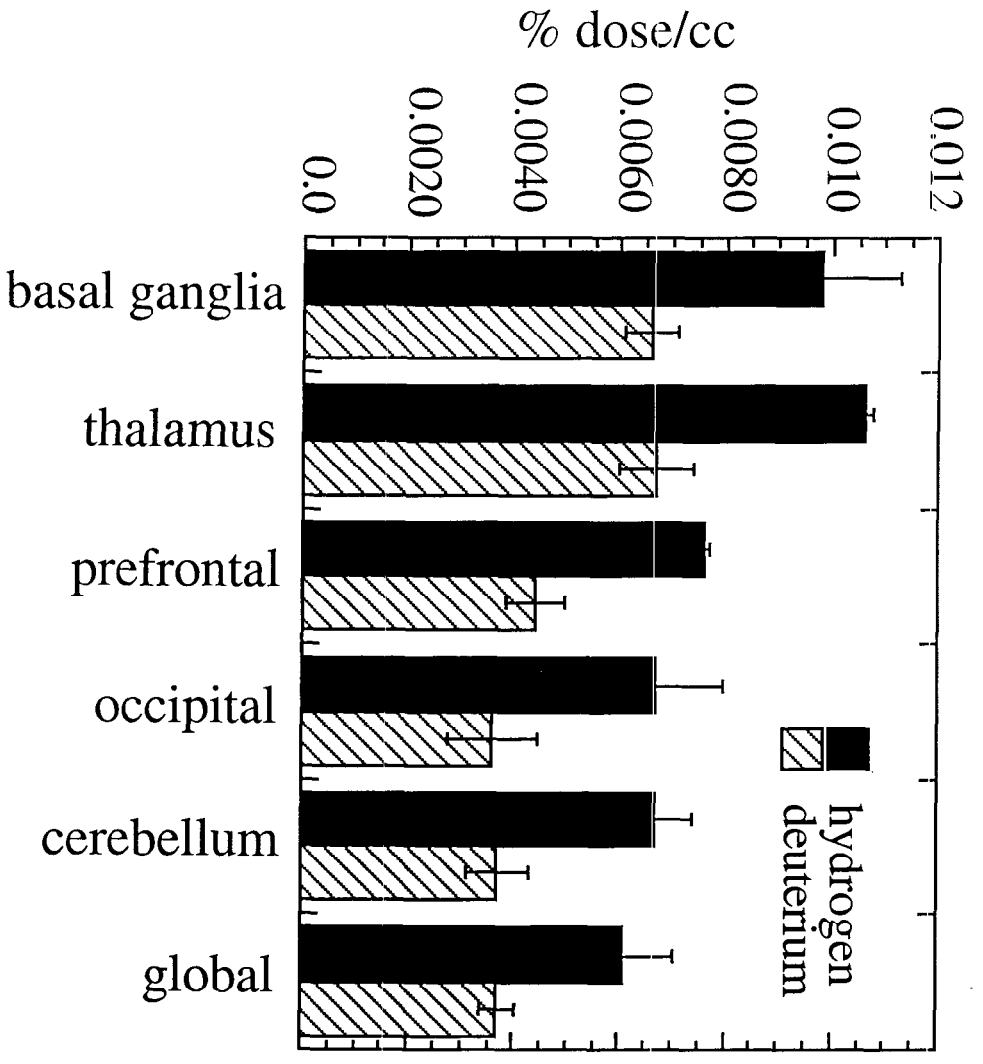


Figure 9. Comparison of the uptake (% injected dose/cc; mean ± sdm) of [^{11}C]L-deprenyl (squares) and [^{11}C]L-deprenyl-D2 (circles) in different regions of the human brain (n=5) (Fowler et al., 1995).

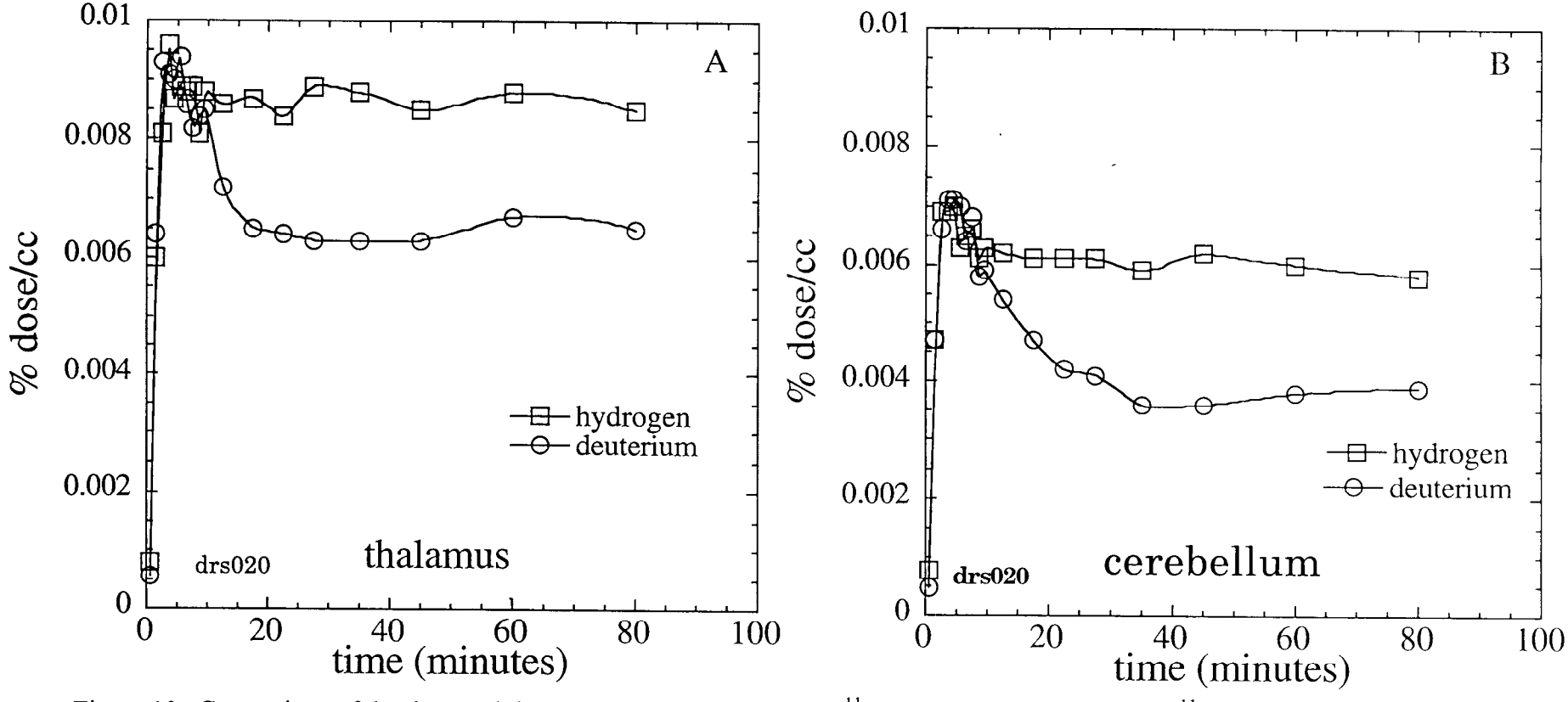


Figure 10. Comparison of the time-activity curves for one subject for [^{11}C]L-deprenyl (squares) and [^{11}C]L-deprenyl-D2 (circles) in the human thalamus (A) and cerebellum (B) (Fowler et al., 1995).

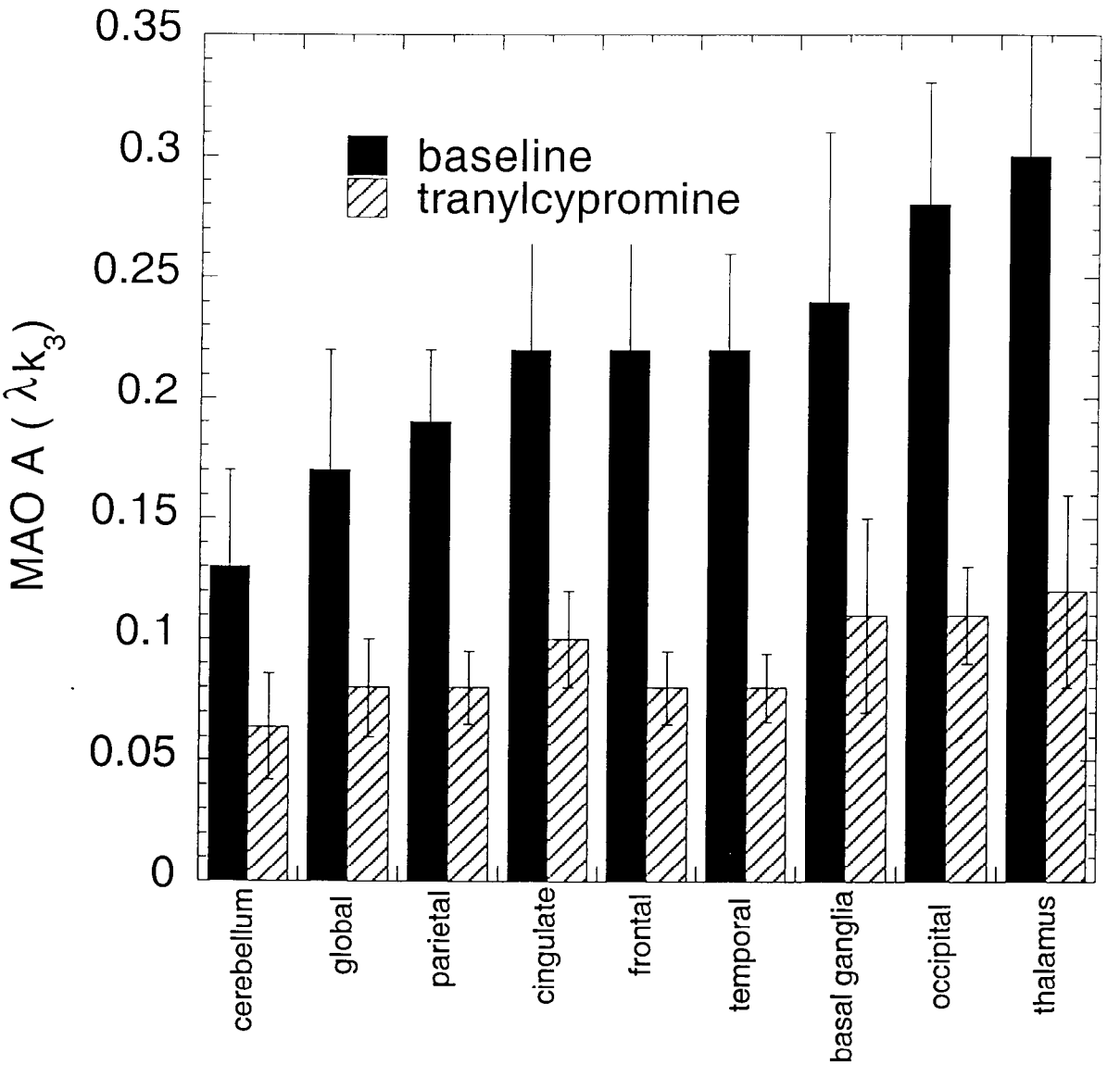
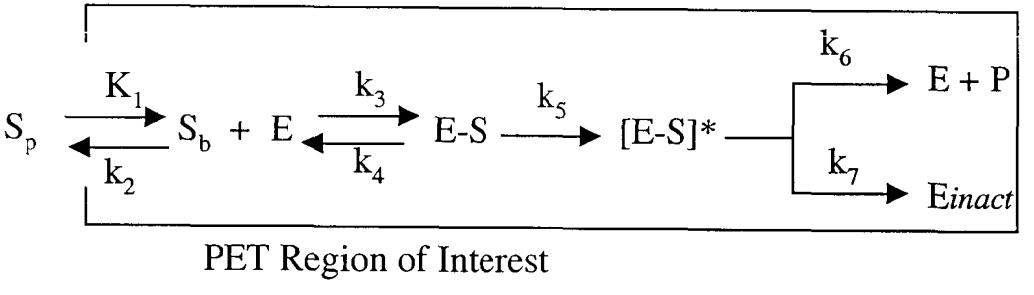
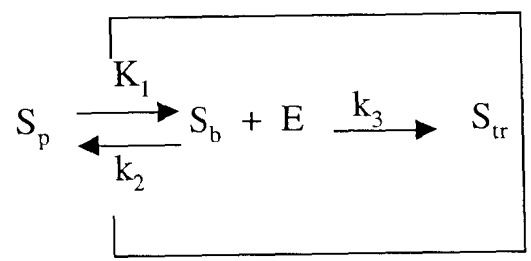


Figure 11. Comparison of MAO A (as represented by the model term λk_3) for four healthy volunteers at baseline and after the non-selective MAO inhibitor drug tranylcypromine (10 mg/day) for 3 days (Fowler et al., 1996b).

Fig 11



PET Region of Interest



PET Region of Interest

Table 1

Table 1. Comparison of λk_3 and K_1 for different brain regions for [^{11}C]L-deprenyl-D2

Brain Region	MAO B (λk_3)		Blood Flow (K_1)	
	r	p	r	p
global	+0.74	0.0001	-0.62	0.003
cingulate gyrus	0.09	0.71	-0.78	0.0001
pons	+0.64	0.003	-0.3	0.2
basal ganglia	+0.67	0.0008	-0.57	0.006
thalamus	+0.71	0.0003	-0.53	0.01
frontal cortex	+0.66	0.001	-0.76	0.0001
cerebellum	+0.65	0.002	0.14	0.02
parietal cortex	+0.48	0.03	-0.68	0.0006
temporal cortex	+0.60	0.004	-0.72	0.0003

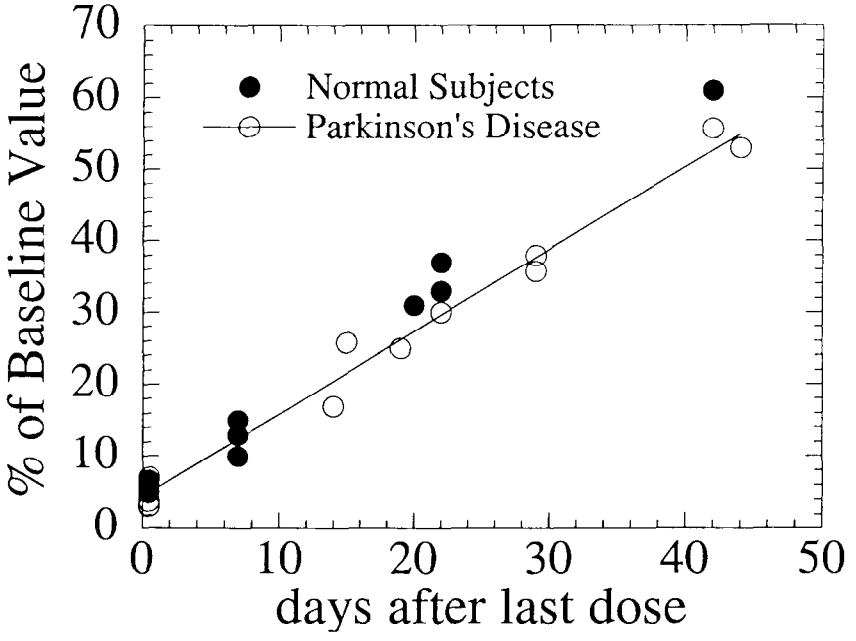


Figure 12. Recovery of brain MAO B activity in elderly normal subjects and in patients with Parkinson's disease after withdrawal from L-deprenyl, which had been given for 1 week (10 mg/day). PET measures of MAO B using [^{11}C]L-deprenyl at various times after the last dose of L-deprenyl allowed the calculation of the half-time for MAO B synthesis in the brain (about 40 days) (Fowler et al., 1994).

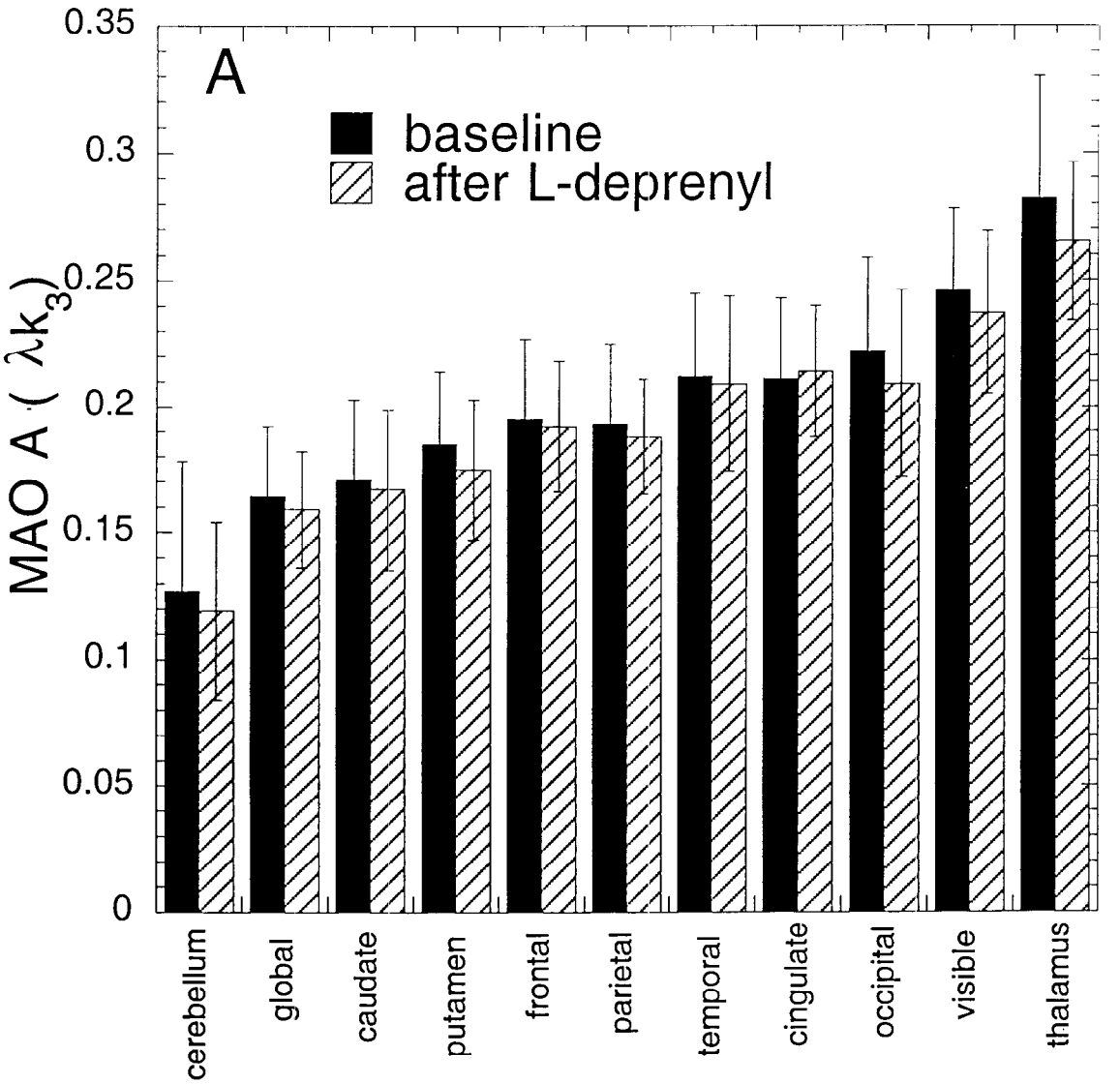


Figure 13. Comparison of MAO A (as measured by [^{11}C]clorgyline and as represented by the model term λk_3; mean ±sdm) in different brain regions for six healthy volunteers at baseline and after treatment with the MAO B selective drug L-deprenyl (10 mg/day) for 3 days. There were no significant differences indicating that selectivity for MAO B is maintained for a 1 week treatment period (Fowler et al., 2000c).

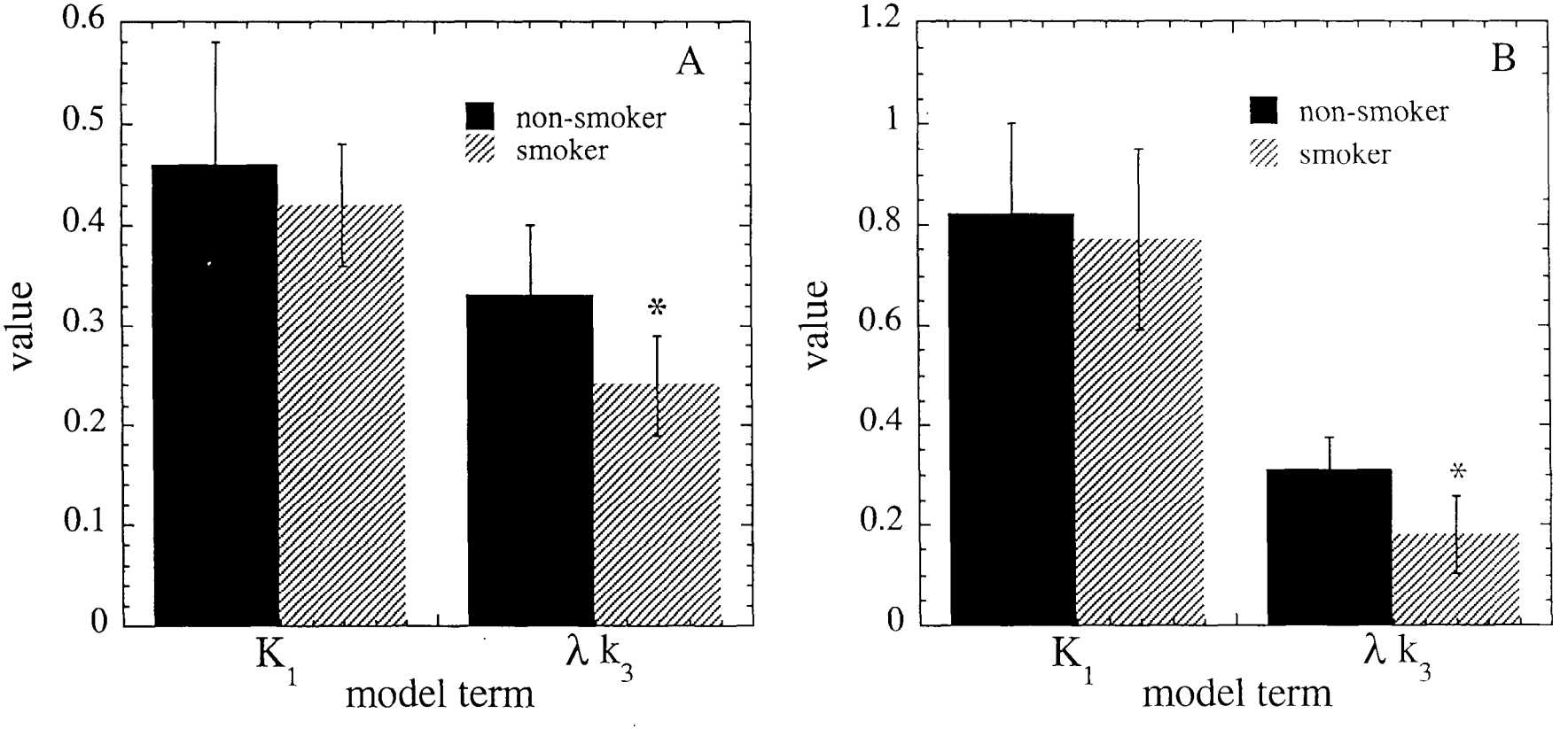


Figure 14. Bar graphs comparing K_1 (plasma to brain transfer constant) and λk_3 (MAO A) (panel A) and MAO B (panel B) in non-smokers and in smokers. Note that there were no significant differences in K_1 while MAO A and B were significantly reduced in the smokers brain (Fowler et al., 1996a,b).