Working against Time: Rapid Radiotracer Synthesis and Imaging the Human Brain

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Introduction

Over 60 years ago, Lauritsen and Crane discovered carbon-11, a new radioactive isotope which has a 20.4 min half-life and decays by positron emission. Since this preceded the discovery of carbon-14 by several years, carbon-11 became the first radioactive isotope of carbon to be used for chemical and biochemical tracer studies prior to and during World War II.[1] Because of the extraordinary experimental limitations imposed by the 20.4 min half-life, carbon-11 was largely replaced by the longer lived carbon-14 which became available after World War II. Ironically, interest in carbon-11 and three other short-lived positron emitters (fluorine-18, nitrogen-13, oxygen-15; Table 1) was rekindled two decades later when it was realized that their short half-lives and body-penetrating radiation resulting from positron decay provided the potential to image biochemical transformations in the living human body with a very low radiation dose.[2] This stimulated the study of the chemistry of the short-lived positron emitters as well as the development of positron emission tomography (PET), a medical imaging method for measuring the spatial and temporal distribution of the positron emitters in the human body by coincidence detection of the annihilation photons resulting from positron decay.[3] Over the past 30 years, advances in synthetic chemistry and PET instrumentation have merged to make PET a powerful scientific tool for studying biochemical transformations and the movement of drugs in the human brain as well as other organs in the body.

Time dominates all aspects of a PET study. In essence, PET radiotracers must be synthesized and imaged within a time frame compatible with the half-life of the isotope. For carbon-11, this typically amounts to about 10 min for isotope production, 40 min for radiotracer synthesis, and up to about 90 min for PET imaging. Thus, the entire study must be orchestrated and carried out within about 2.5 h. Studies of brain activation where the aim is to determine which areas of the brain are active during the performance of a specific task present an extreme example.[4] Here oxygen-15-labeled water or oxygen-15-labeled butanol (synthesized via organoborane chemistry[5]) is used to measure brain blood flow. Because oxygen-15 has a 2 min half-life, an entire measurement is accomplished in under 5 min.

In this Account, we describe some advances in radiotracer chemistry which have made it possible to probe the chemical anatomy of the human brain while working within a very restricted time scale. Though we highlight research from our laboratory, it is important to emphasize that advances in PET brain imaging have come from many laboratories throughout the world. Thus, for a more comprehensive treatment of PET technology the reader is referred to textbooks and review articles cited in this Account. Since many of the milestones in delineating biochemical transformations and the movement of drugs in the human brain have involved radiosynthesis with carbon-11 and fluorine-18, we focus on these two isotopes.

Rapid Chemistry

A few general comments are required to provide a context for a discussion of rapid radiotracer synthesis. For all practical purposes, the synthesis of a C-11- or an F-18-labeled tracer must be accomplished within 2 half-lives after the isotope is produced. Large amounts of radioactivity need to be used in order to compensate for radioactive decay and for the sometimes low synthetic yields, and thus shielding, remote operations, and automation are integrated into the experimental design.[6] Syntheses frequently involve multiple steps, and the crude reaction mixture is usually purified by HPLC. Since radiotracers are typically administered intravenously, procedures must be developed to yield radiotracers which are sterile and pyrogen free.[7]

Carbon-11 and Fluorine-18 Production. Between 1950 and the mid-1970s, a small number of chemists studied the pure chemistry of radioactive atoms such as carbon-11. Basic research in "hot atom chemistry", as it came to be known, provided the knowledge to control the chemical form of the short-lived positron emitters and set the stage for producing the short-lived positron emitters in chemical forms which were useful for the synthesis of complex radiotracers.[1] Because of the short half-lives,

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Table 1. Physical Properties of the Short-Lived Positron Emitters

isotope	half-life (min)	specific activity[a] (Ci/mmol)	maximum energy (MeV)	range (mm) in H_2O[b]	decay product
fluorine-18	110	1.71×10^6	0.635	2.4	oxygen-18
carbon-11	20.4	9.22×10^6	0.96	4.1	boron-11
oxygen-15	2.1	9.08×10^7	1.72	8.2	nitrogen-15
nitrogen-13	9.96	1.89×10^7	1.19	5.4	carbon-13

[a] Theoretical maximum; in reality the measured specific activities of ^{11}C, ^{18}F, ^{13}N, and ^{15}O are ca. 5000 times lower because of unavoidable dilution with the stable element. [b] Maximum linear range.

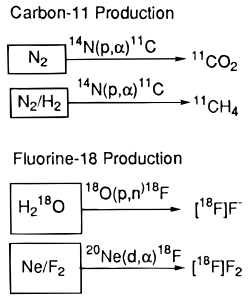

FIGURE 1. Common nuclear reactions and target materials for carbon-11 and fluorine-18 production.

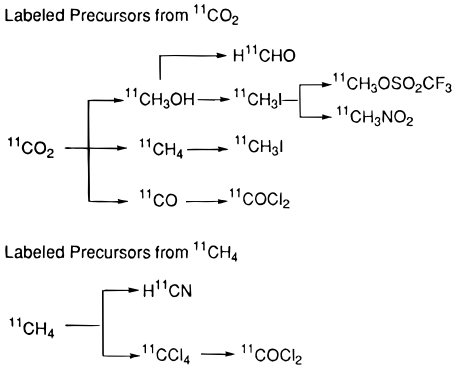

FIGURE 2. Some carbon-11-labeled precursors synthesized from $^{11}CO_2$ and $^{11}CH_4$.

each radiotracer synthesis usually begins with the production of the isotope. This involves bombarding appropriate stable (and sometimes enriched) isotopes with charged particles such as protons and deuterons which are most commonly and conveniently produced using a cyclotron or other accelerator. Three nuclear reactions, the $^{14}N(p,\alpha)^{11}C$, the $^{18}O(p,n)^{18}F$, and the $^{20}Ne(d,\alpha)^{18}F$ reactions, are most commonly used for carbon-11 and fluorine-18 production (Figure 1).[8]

An important point is that the substrate that is used for the nuclear reaction (referred to as the "target") is usually a different element than the radioisotope produced. Carbon-11, for example, is produced from the cyclotron bombardment of stable nitrogen ($^{14}N(p,\alpha)^{11}C$). Because stable carbon is ubiquitous in nature, it is not possible to remove it completely from the target and from the reagents used in the synthesis. Thus, it is typical that the ^{12}C:^{11}C ratio is about 5000:1. Even with this dilution, the specific activity (units of radioactivity/unit of mass) of PET radiotracers is usually very high (Table 1). Syntheses are always carried out on a micro- or a semimicroscale, and typical chemical masses associated with PET radiotracers are a few micrograms or less. High specific activity provides the opportunity for imaging biological substrates such as neurotransmitter receptors at tracer concentrations.[9] However, the chemical mass which constitutes a tracer dose depends on the process being measured. For example, biological targets such as neurotransmitter receptors usually occur at much lower concentrations than enzymes, and thus higher specific activities are required for receptor studies.

Fluorine-18 is most commonly produced by bombarding oxygen-18-enriched water with protons to yield [^{18}F]-fluoride. As is the case with carbon-11, it is not possible to remove all stable fluoride ion from the target materials and from the reagents used in the synthesis so that the isotope is always diluted with stable fluoride. In contrast to [^{18}F]fluoride, which is always produced without the *intentional* addition of stable fluoride, [^{18}F]F_2 is always purposely diluted with unlabeled F_2.[10] In general, for equal amounts of radioactivity, the chemical mass associated with an [^{18}F]F_2-derived radiotracer (carrier added) exceeds that of an [^{18}F]fluoride ion-derived radiotracer (no carrier added) by a factor of 1000. The need for a high specific activity electrophilic fluorination reagent has been an important goal in radiotracer research, and there has been some recent progress in achieving high specific activity F-18-labeled acetyl hypofluorite using [^{18}F]fluoride from an enriched water target and a very small quantity of elemental fluorine (280 nmol).[11]

Carbon-11-Labeled Compounds. The difficulties in carbon-11 synthesis which are imposed by the 20.4 min half-life are magnified by the fact that only $^{11}CO_2$ and $^{11}CH_4$ come directly from the cyclotron target using properly adjusted radiation conditions (Figure 1).[12] A number of other precursor molecules, some of which are shown in Figure 2, are synthesized from labeled carbon dioxide or methane, but all require some synthetic manipulation during or after cyclotron bombardment.

Some of the earliest syntheses with carbon-11 depended directly on labeled carbon dioxide and labeled cyanide.[1,8] Today, however, alkylation with [^{11}C]methyl iodide is the most widely used method for introducing carbon-11 into organic molecules.[13] Alkylations are generally straightforward, though frequently the reaction substrate must be prepared with protecting groups which can be rapidly removed. This approach is illustrated by

(8) For specific references see: Fowler, J. S.; Wolf, A. P. In *Positron Computed Tomography*; Phelps, M., Mazziotta, J., Schelbert, H., Eds.; Raven Press: New York, 1986; pp 391−450.
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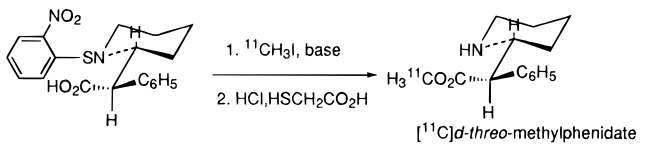
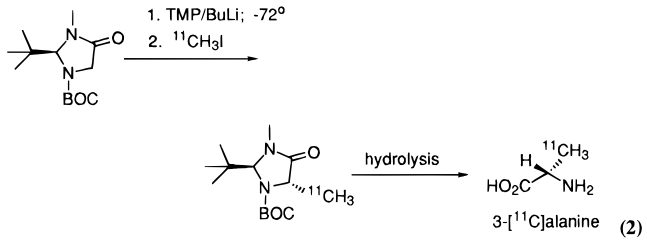
the 45 min synthesis of [^{11}C]*d-threo*-(or *l-threo*-)methylphenidate) from labeled methyl iodide and a protected derivative of *d*- or *l-threo*-ritalinic acid (eq 1).[14] In the



(1)

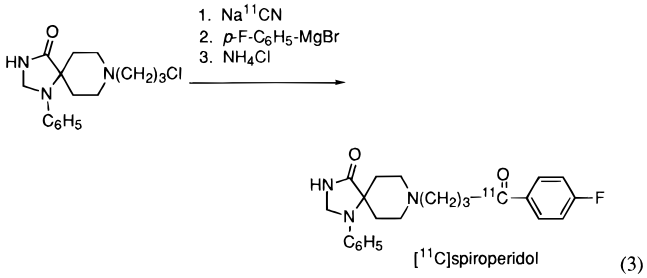
case of relatively unstable compounds, [^{11}C]methylation can be carried out under milder conditions using [^{11}C]-methyl triflate.[15] The recent introduction of an on-line gas phase synthesis to give high specific activity $^{11}CH_3I$ from labeled methane is a promising new development.[16]

Carbon-11 synthesis is frequently complicated by the need for chiral labeled products. In the case of radiotracers like [^{11}C]*d-threo*-methylphenidate described above, this is readily accomplished because the chiral center is present in the substrate (*d*-ritalinic acid) and the reaction conditions preserve the chirality. However, asymmetric syntheses have also been developed. For example, enantiomerically enriched [3-^{11}C]L-alanine was synthesized from $^{11}CO_2$ (via methyl iodide; eq 2).[17]



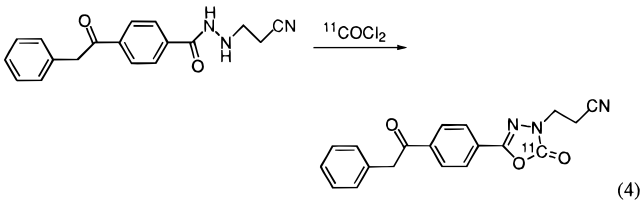
(2)

Labeled methane is also very useful in synthesis because it is available in large quantities and can be readily converted to H^{11}CN by passing the target gas (N_2/H_2 plus a small quantity of radiolytically produced ammonia) over platinum wool at 1000 °C. It has been used in the synthesis of labeled amines, ketones, aldehydes, acids, and amino acids.[8] For example, it was used in a two-step, 40 min synthesis of [^{11}C]spiroperidol (in 20−30% radiochemical yield based on [^{11}C]cyanide and corrected for radioactive decay) for early studies of the dopamine D2 receptor (eq 3).[18] Labeled methane has also



(3)

been converted to [^{11}C]phosgene which has been used in the synthesis of many compounds including a ring-labeled monoamine oxidase inhibitor (eq 4).[19]



(4)

Problems in carbon-11 synthesis generally include rigorously excluding stable carbon in order to maximize the specific activity of the product, optimizing reaction rates and developing chromatographic methods which separate the labeled product from starting materials and byproducts. Reaction times have been reduced and yields have been increased for many labeled compounds by applying microwave technology.[20]

Fluorine-18-Labeled Compounds. Whereas the 20 min half-life of carbon-11 requires that the entire synthesis be accomplished in about 40 min, fluorine-18's 110 min half-life allows more time for relatively complex synthetic manipulations and for biological studies. An additional advantage is that fluorine-18 has the lowest positron energy, and thus its maximum range (2.4 mm) allows for the sharpest imaging with a high-resolution PET (Table 1). Disadvantages relative to carbon-11 include the fact that fluorine is a foreign element to most biological molecules and the fact that the 110 min half-life precludes the performance of multiple studies on the same subject on the same day.

There are two simple labeled forms of F-18 (fluoride ion and elemental fluorine) which are directly available for radiotracer synthesis. Fluoride ion is the more desirable of the two because it can be produced in high yield and without added carrier. In principle, 100% of the isotope can be incorporated into the tracer. In contrast, the maximum radiochemical yield when [^{18}F]F_2 is used as a precursor is usually only 50%, because only one of the fluorine atoms in the fluorine molecule is labeled and typically only one atom of fluorine is incorporated. This loss of 50% of the label also applies when labeled fluorine is converted to other precursors like labeled acetyl hypofluorite.[12] 2-Deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) is a widely used radiotracer developed in our laboratory in 1976 and used to measure glucose metabolism. It exemplifies the evolution and improvement of a synthesis through time (Figure 3). [^{18}F]FDG was first synthesized by the electrophilic fluorination with [^{18}F]F_2, and an improved synthesis from acetyl [^{18}F]hypofluorite was reported a few years later.[21,22] A nucleophilic substitution with [^{18}F]fluoride was reported in 1986.[23] It gave signifi-

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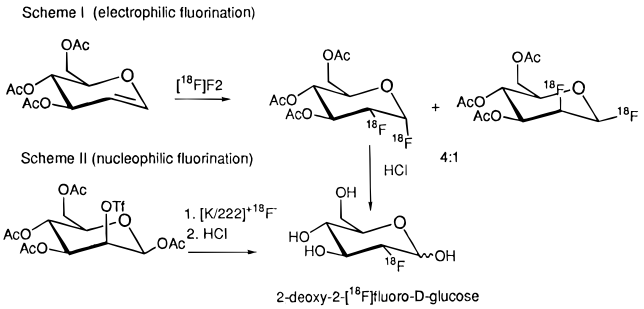
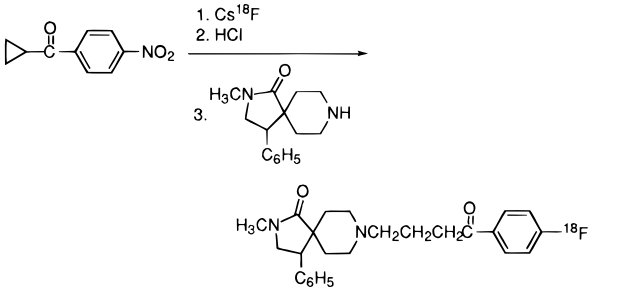


FIGURE 3. Electrophilic and nucleophilic routes to [^{18}F]FDG.

cantly higher yields and has largely replaced the electrophilic route. Though some radiotracers such as [^{18}F]-fluoro-DOPA (6-[^{18}F]fluoro-3,4-dihydroxyphenylalanine)[24] are still more conveniently synthesized from [^{18}F]F_2 or acetyl [^{18}F]hypofluorite,[25] most F-18-labeled radiotracers including [^{18}F]fluoro-DOPA can now be prepared from [^{18}F]fluoride ion.

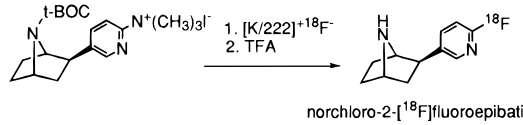
The most successful approach for preparing high specific activity ^{18}F-substituted aromatic compounds is the nucleophilic aromatic substitution reaction.[10,26] The minimal structural requirements for efficient nucleophilic aromatic substitution are the presence of an electron-withdrawing, activating substituent such as RCO, CN, NO_2, etc., as well as a leaving group, such as nitro- or trimethylammonium. A multistep 2 h synthesis of [^{18}F]*N*-methylspiroperidol for measuring dopamine D2 receptors is shown (eq 5).[27] It is noteworthy that *N*-methylspiroperidol



(5)

has also been labeled with carbon-11.[28] This multistep sequence contrasts with the one-pot, two-step synthesis of [^{18}F]fluoroepibatidine, a radiotracer with high specificity for nicotinic acetylcholine receptors and which is synthesized in high radiochemical yield (70%) using the nucleophilic heteroaromatic substitution reaction (eq 6).[29]

In addition to simple fluorine-substituted aromatic compounds, there are important radiotracers with electron-donating substituents on the aromatic ring which can impede the nucleophilic aromatic substitution reaction. Recent mechanistic studies in our laboratory have established that nucleophilic aromatic substitution can be carried out in the presence of suitably protected electron-donating groups, thus extending the utility of the nucleophilic aromatic substitution to the synthesis of 6-[^{18}F]-fluoro-DOPA as well as 6-[^{18}F]fluorodopamine and (+)- and (−)-6-[^{18}F]fluorononorepinephrine (eq 7) in sufficiently



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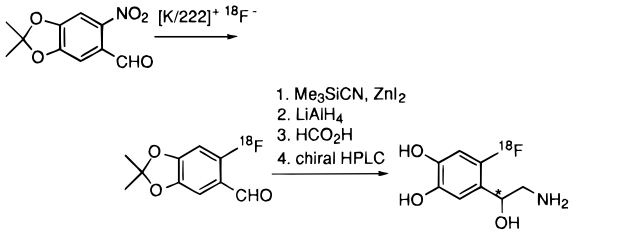

(7)

high specific activity for tracer studies.[30,31]

Radiotracer Design and Mechanisms. Radiotracer design is complicated by the fact that it is not possible to predict completely the behavior of an organic compound in the human body. However, studies in animals and in isolated tissues can guide the process. In addition, the physical properties of the compounds such as their lipophilicity[32] and potential pitfalls such as rapid metabolism[33] and binding to plasma proteins[34] also come into play. Because a PET image provides no information on the chemical compound(s) giving rise to the image or on the cellular or subcellular localization or binding site, pharmacological intervention as well as the tools of mechanistic organic and biochemistry is also commonly used to interrogate the image. These include the use of stereoselectivity,[35] deuterium isotope effects,[31,36] and/or an examination of the behavior of the same compound labeled in different positions.[37] Occasionally the position of the label must be adjusted[38] or structural modifications[39] made to simplify the profile of labeled metabolites contributing to the image. Radiotracer kinetics can also

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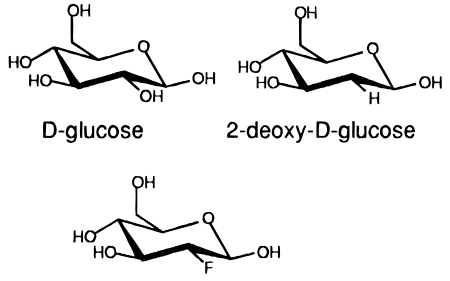
be a limiting factor in quantitation and therefore must be critically examined and appropriate kinetic models developed to calculate parameters which are related to receptor concentration, enzyme activity, or some other factor.[3]

Imaging the Human Brain

Brain Glucose Metabolism. Almost all of the brain's energy derives from glucose metabolism, and thus the development in 1976 of [^{18}F]FDG, a radiotracer which measures brain glucose metabolism, had a profound influence on research in the neurosciences and on the evolution of PET.[22] [^{18}F]FDG was modeled after carbon-14-labeled 2-deoxyglucose ([^{14}C]2DG), a tracer used to



measure brain glucose metabolism in animals. In [^{18}F]-FDG, a radioactive fluorine atom replaces the hydroxyl group on carbon-2 of glucose. We selected C-2 for fluorine substitution because only the C-2 hydroxyl group on glucose can be removed and still retain the ability of the molecule to be a substrate for hexokinase (the rate-limiting enzyme in glycolysis). A key feature is the hexokinase-catalyzed conversion of [^{18}F]FDG to [^{18}F]FDG-6-phosphate which is trapped in the cell where metabolism has occurred (Figure 4). When imaged, metabolically trapped [^{18}F]FDG-6-phosphate provides a map of glucose metabolism in all areas of the brain simultaneously.

[^{18}F]FDG is still the most widely used PET tracer in the world. It is used to measure glucose metabolism in the brain and to map drug- or disease-related changes in metabolism. It is the workhorse of PET for basic studies in the clinical neurosciences. It is also used as a tool in clinical diagnosis in heart disease, epilepsy, and cancer, demonstrating the impact of basic research on clinical practice.[40]

Drug Pharmacokinetics and Pharmacodynamics

One of the most fruitful applications of PET in recent years has been in the study of therapeutic drugs and substances of abuse.[41] PET is used to measure directly drug pharmacokinetics (using the labeled drug) or drug pharmacodynamics (using a tracer like [^{18}F]FDG). It is also used to determine drug mechanisms and their relationship to

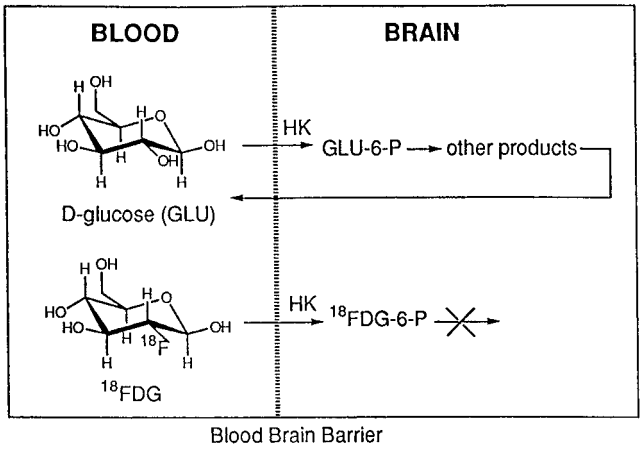


FIGURE 4. Simplified diagram comparing the behavior of glucose and 2-deoxy-2-fluoro-D-glucose in the brain. Glucose crosses the blood brain barrier by facilitated transport and enters a cell. There it enters the glycolytic cycle where it is first phosphorylated by hexokinase (HK) and eventually produces adenosine triphosphate (ATP) and metabolites which can leave the cell. Like glucose, [^{18}F]FDG also undergoes facilitated transport into the brain and is phosphorylated by hexokinase to produce [^{18}F]FDG-6-phosphate ([^{18}F]FDG-6-P). However, [^{18}F]FDG-6-P does not undergo further metabolism and is trapped in the cell.

the behavioral and therapeutic properties of the drug. In this respect PET is absolutely unique. No other technology is capable of probing drug behavior in humans as rapidly, as safely, and as precisely as PET. We will highlight our studies on two classes of drugs, the psychostimulants, and the monoamine oxidase (MAO) inhibitors.

Psychostimulant Drugs: Cocaine and Methylphenidate. As a class, psychostimulants generally increase alertness and motor activity and decrease fatigue and appetite. There is substantial evidence that these drugs act by increasing the synaptic concentration of dopamine (3,4-dihydroxyphenethylamine), a neurotransmitter which is crucial in motivation, movement, and reward. For example, cocaine increases dopamine by blocking the dopamine transporter, thereby impeding the reuptake of dopamine from the synapse. This cocaine-induced increase in synaptic dopamine is believed to be responsible for the "high" (Figure 5a).[42]

Cocaine stands apart from other psychostimulants in terms of its powerful addictive properties. In order to probe the extent to which the distribution and kinetics of cocaine is associated with its behavioral effects, we labeled cocaine with carbon-11 and obtained the first images of the distribution and kinetics of cocaine in the human brain in 1988.[43] Cocaine had a remarkably high and rapid uptake in the basal ganglia, a brain region with a high density of dopamine transporters. However, it also had a surprisingly rapid clearance from the brain. This rapid uptake and clearance of a tracer dose of labeled cocaine almost perfectly paralleled the high from a behaviorally active dose of cocaine (about 40 mg), providing strong evidence that transporter occupancy by cocaine is associated with its behavioral effects (Figure 5b).

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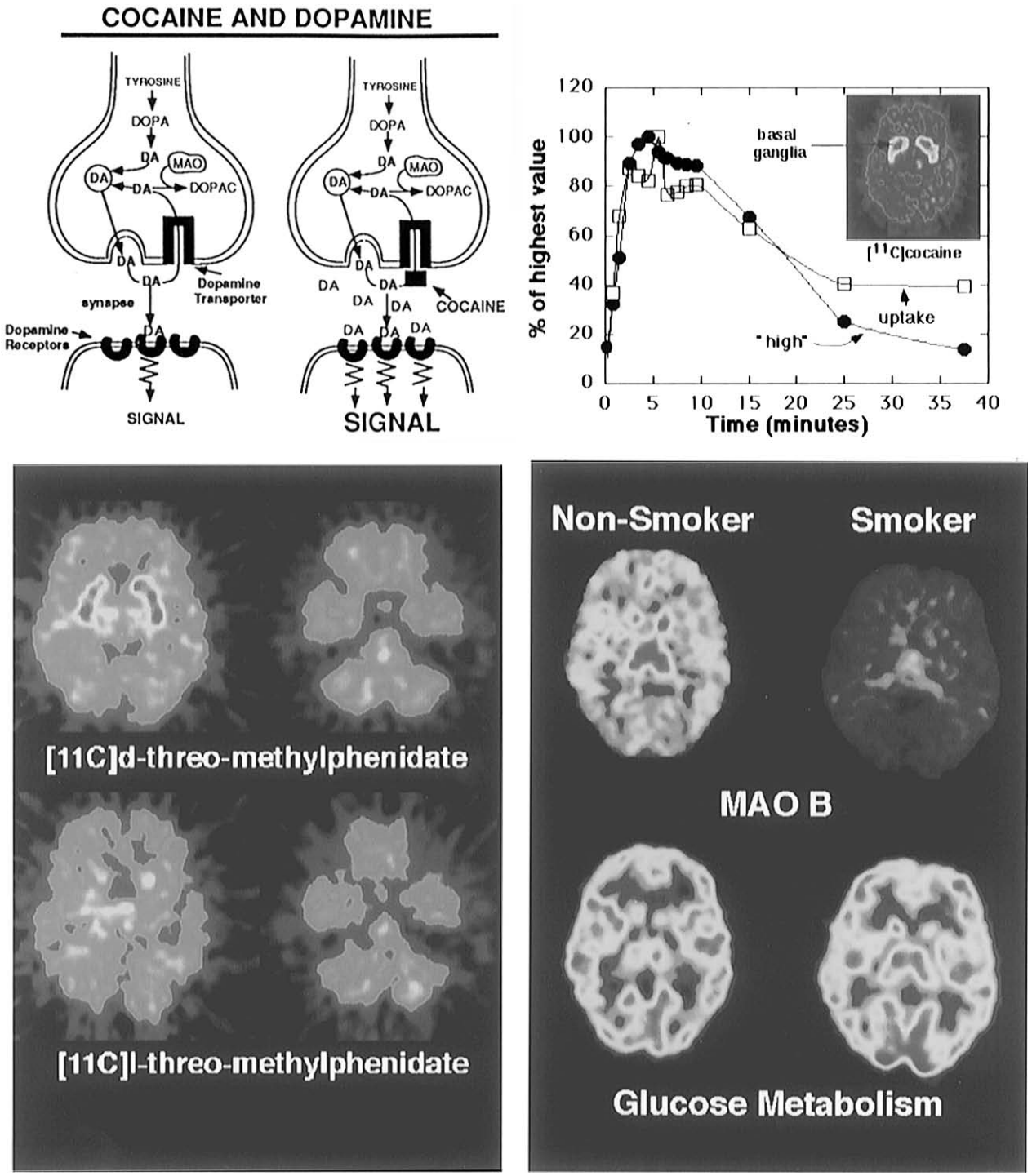

FIGURE 5. (a, top left) Simplified diagram showing the interaction of cocaine with the dopamine neuron. Dopamine (DA) is synthesized in the dopamine neuron. When the neuron is stimulated, DA is released into the synapse where it binds to a dopamine receptor on the postsynaptic neuron, producing a signal. The concentration of DA in the synapse is regulated by a number of mechanisms, the most important of which is reuptake into the presynaptic cell via the dopamine transporter. Reuptake is blocked by drugs such as cocaine and methylphenidate which results in an increase in synaptic DA. (b, top right) An image of [^{11}C]cocaine in the human brain at the level of the basal ganglia along with the time course of the uptake and clearance drug in the brain (open squares) and the time course of the cocaine-induced high (closed circles). (c, bottom left) Comparison of [^{11}C]*d-threo*-methylphenidate (active enantiomer: top images) and [^{11}C]*l-threo*-methylphenidate (inactive enantiomer: bottom images) in the human brain at the level of the basal ganglia (left) which has a high concentration of dopamine transporters and the cerebellum (right) which has negligible dopamine transporters. (d, bottom right) Comparison of MAO B activity as measured by [^{11}C]L-deprenyl-d_2 and glucose metabolism as measured by [^{18}F]FDG in a nonsmoker and in a smoker at the level of the thalamus. Note that the smoker has reduced MAO B activity relative to the nonsmoker but that the nonsmoker and the smoker have similar brain glucose metabolism.

Methylphenidate is another psychostimulant drug that binds to the dopamine transporter. However, in contrast to cocaine, methylphenidate (Ritalin) is used therapeutically to treat attention deficit disorder and narcolepsy. It is the most commonly prescribed psychotropic medication for children in the United States. Methylphenidate is marketed as the racemic form (*d,l-threo*-methylphenidate) even though the pharmacological activity is known to reside in the *d-threo* form. Studies in our laboratory comparing [^{11}C]*d-threo*- and [^{11}C]*l-threo*-methylphenidate

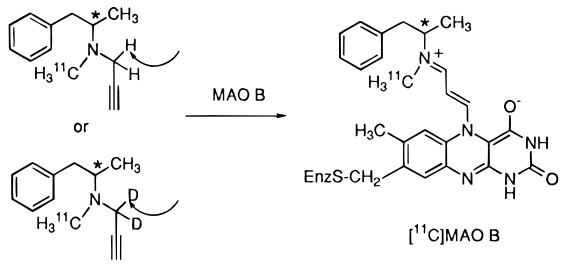

FIGURE 6. Simplified diagram depicting the *in vivo* labeling of MAO B using [^{11}C]L-deprenyl or deuterium-substituted [^{11}C]L-deprenyl ([^{11}C]L-deprenyl-d_2). Arrows point to the C−H (C−D) bond which is cleaved.

in the human brain showed that *d-threo*-methylphenidate is retained in the basal ganglia which has a high concentration of dopamine transporters while *l-threo*-methylphenidate which has low affinity for the transporter clears rapidly and shows no specific retention (Figure 5c).[44] This study allowed for the first time the direct comparison of the two enantiomers in the human brain, clearly demonstrating that specificity lies in the *d-threo* enantiomer.

We are currently using [^{11}C]cocaine and [^{11}C]methylphenidate to examine the relationship between dopamine transporter occupancy and the high with a view to developing effective treatments for the cocaine abuser.[45]

Monoamine Oxidase Inhibitors. Monoamine oxidase (MAO) is a flavin-containing enzyme which exists in two subtypes (MAO A and B) and which oxidizes amines including dopamine and other neurotransmitters according to eq 8.[46] Medical interest in MAO stems from the

$$RCH_2NH_2 + O_2 + H_2O \rightarrow RCHO + H_2O_2 + NH_3 \quad (8)$$

utility of MAO inhibitor drugs in the treatment of depression and Parkinson's disease. Our interest in MAO grew out of an investigation of whether the principle of suicide enzyme inactivation[47] could be used to covalently label and image an enzyme *in vivo* (Figure 6). This proved to be feasible, and the first images of functional MAO activity in the human brain were made carbon-11-labeled suicide enzyme inactivators ([^{11}C]clorgyline and [^{11}C]L-deprenyl.[35] Mechanistic PET studies with deuterium-substituted [^{11}C]-L-deprenyl demonstrated that the C−H bond in the propargyl group was involved in the rate-limiting step for the formation of the PET image and provided a means of selectively controlling the rate of trapping of tracer in the brain to improve quantitation.[36]

We used [^{11}C]L-deprenyl and the deuterium-substituted derivative to directly examine the effects of MAO B inhibitor drugs in the human brain. For example, labeled L-deprenyl was used to determine the minimum effective dose of lazabemide (*N*-(2-aminoethyl)-5-chloropicolinamide), a new MAO B inhibitor drug for treating Parkinson's disease.[48] This information facilitated the introduction of lazabemide into clinical practice by providing the required dosing information for clinical trials. We also used labeled deprenyl to directly measure the synthesis rate for MAO B in the human brain after it had been irreversibly inhibited by a therapeutic dose of L-deprenyl (which is used to treat Parkinson's disease).[49] In this study it was determined that the *half-life* for enzyme recovery after the last dose of L-deprenyl was 40 days! This was the first time that the synthesis rate of a specific protein was measured directly in the living human brain. The slow recovery of brain MAO B suggests that the current clinical dose of L-deprenyl may be excessive and that the clinical efficacy of a reduced dose should be evaluated. Such an evaluation may have mechanistic importance and may also reduce the costs and side effects associated with excessive drug use.

A particularly fascinating observation emerged from our PET studies of MAO B in the normal human brain using deuterium-substituted [^{11}C]L-deprenyl. Certain normal individuals had brain MAO B levels which resembled individuals receiving MAO B inhibitor drugs like L-deprenyl or lazabemide. The mysteriously low MAO B levels were traced to cigarette smoking. Subsequent PET studies showed that smokers have an average of 40% lower brain MAO B than nonsmokers and former smokers (Figure 5d).[50] The fact that former smokers have normal MAO B levels points to a pharmacological rather than a genetic effect. Interestingly, the MAO B inhibitory constituent(s) in smoke is not nicotine since nicotine does not inhibit MAO B at physiologically relevant concentrations. Reduced brain MAO in smokers may be an important neurochemical link to smoking epidemiology. For example, smokers have a lower risk for developing Parkinson's disease than nonsmokers. Since hydrogen peroxide is a byproduct of MAO-catalyzed oxidation of amines (eq 8), MAO inhibition by smoke may result in reduced levels of hydrogen peroxide and reduced oxidative stress. This study raises new issues relative to the neuropharmacological actions of tobacco smoke exposure and illustrates the power of PET to add to knowledge of the human brain.

Outlook

Modern day PET research is enriched and strengthened from the integration of many disciplines. However, it is advances in radiotracer chemistry which have played the pivotal role in driving the field in new directions in the study of the human brain. At the heart of this development is synthetic chemistry directed to the rapid incorporation of simple short-lived precursor molecules into organic compounds and drugs which can be used to map

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specific processes. Advances in organic synthesis can have a potentially important impact on neuroimaging and diagnosis in cancer and heart disease, especially advances in the rapid microscale, on-line conversion of simple C-1 compounds like methane and carbon dioxide to useful precursors for organic synthesis and in the development of simple methods for high specific activity electrophilic fluorination. Perhaps the greatest challenge is to advance our understanding of the interactions between chemical compounds and living systems. For example, we are just scratching the surface relative to understanding the complexities in designing labeled molecules with biologic and kinetic properties which allow the visualization of a single biochemical process in a system where all of the chemical reactions of life are occurring. There is also a need to develop synthetic routes to the positron-emitter-labeled versions of important therapeutic drugs. In this regard, PET is a sufficiently important tool in drug research and development to be considered in the actual drug design process to say nothing of drug development costs obviated by PET results. For example, the deliberate incorporation of a fluorine atom into a drug molecule for eventual F-18 labeling for PET studies, or design drug molecules with carbon-11 labeling in mind, would permit the determination of the short-term distribution and pharmacokinetics of the drug in the human body. One of the payoffs would be the ability to determine drug concentration and kinetics directly in the human brain. In fact, PET is the only way to determine whether and how much of a drug enters into the human brain. Because PET studies are possible in humans, the unique ability of humans to describe how they feel permits a new dimension, that of understanding the link between brain chemistry and behavior.

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