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FLUORINE-18 LABELED TRACERS FOR PET STUDIES IN THE NEUROSCIENCES

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Fluorine-18 is a positron emitting isotope of fluorine. It has the longest half-life (110 minute) and the lowest positron energy (0.635 Mev) of the four common positron emitters for positron emission tomography (PET). PET, in conjunction with appropriate radiotracers labeled with fluorine-18, has been used to assess functional activity, biochemical transformations and drug pharmacokinetics and pharmacodynamics in the human and animal body. The PET method, F-18 labeling of organic molecules, and some of the applications of F-18 labeled compounds in the neurosciences (brain and heart) are described.

Positron Emission Tomography (PET) is an imaging method which uses short-lived positron emitting isotopes to track labeled compounds in the living human and animal body (see Table I for the commonly used positron emitters). In a PET study, a radiotracer labeled with a short-lived positron emitting isotope is administered either by intravenous injection or inhalation and the spatial and temporal distribution of the radioactivity are quantitatively measured using a positron emission tomograph. The short half-life of the PET isotopes and their decay to non-radioactive products combine to make this an imaging method exquisitely suited to the study of biochemical processes and drug action in the living human body. In addition, the positron emitters have very high specific activities (radioactivity/unit of chemical mass) and thus PET studies can be carried out at true tracer doses which avoid perturbing the process being measured.

Table I. Physical properties of the short-lived positron emitters.

Isotope	Half-life (min)	Specific Activity (Ci/mmol)*	Maximum Energy (MeV)	Range (mm) in H_2O**	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

* theoretical maximum; in reality the measured specific activities of ^{11}C,^{18}F, ^{13}N and ^{15}O are ca. 10-10,000 times lower because of unavoidable dilution with the stable element.
** maximum linear range

PET derives its flexibility and scientific versatility from the chemical characteristics and short half-life of positron emitters which allow their incorporation into structurally diverse organic compounds for monitoring biochemical transformations. It has become a powerful tool for basic investigations in the neurosciences and has also been expanded to clinical practice where it provides unique information relative to the management of cancer, epilepsy and cardiovascular disease.[1]

This chapter will focus on fluorine-18, the positron emitter with the longest half-life, the lowest positron energy and probably, the most challenging chemistry. The incorporation of F-18 into organic compounds presents many challenges, including: the need to synthesize and purify the compound within a 2-3 hour time frame; the limited number of labeled precursor molecules; the need to work on a microscale; and the need to produce radiotracers which are chemically and radiochemically pure, sterile and pyrogen-free, and suitable for intravenous injection.

The PET method and F-18 labeling of organic molecules will be described followed by highlights of the applications of F-18 labeled compounds in the neurosciences (brain and heart) and neuropharmacology. For a comprehensive survey of the literature of fluorine-18 and PET, the reader is also referred to other literature on the subject.[2, 3, 4, 5]

PET Imaging

Positron decay is the physical process which is at the heart of PET. A positron is a particle which carries a positive charge and has essentially the same mass as an electron. When it is emitted as a result of the radioactive decay of an unstable radionuclide such as fluorine-18, it travels a short distance from the nucleus, typically about 2-8 mm maximum range. It loses its kinetic energy during this flight and then annihilates with an electron. This results in the creation of two photons of equal energy, i.e. 511 keV, which travel in opposite directions very close to 180° apart (Figure 1). It is the distance between the decaying nucleus and the point of annihilation and the fact that the annihilation photons are not emitted at exactly 180° apart that ultimately limits the spatial resolution possible in PET. Since fluorine-18 has the lowest positron energy of the four common short-lived positron emitters (Table I), the average range of the positron before

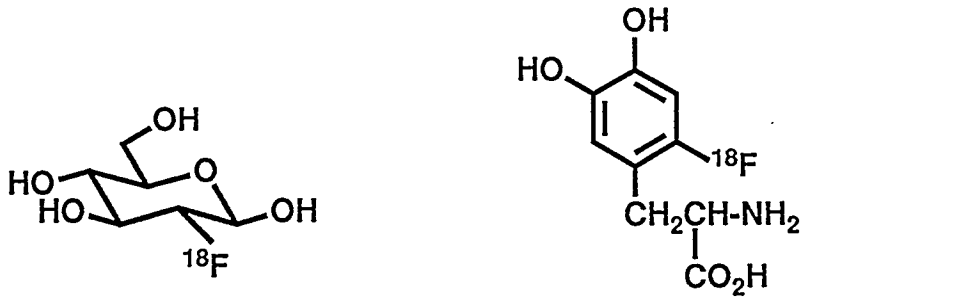
annihilation is shorter compared to the other isotopes. This could affect image resolution with tomographs of very high resolution.[6]

The positron emission tomograph typically consists of a cylindrical array of scintillation crystals, commonly bismuth germinate or sodium iodide, which are designed to register a decay event only when 2 photons enter crystals on opposite sides at essentially the same time, i.e. so called coincidence detection.[7] These events are registered and then processed by an algorithm which allows an image to be reconstructed by computer. The range of resolution of modern PET instruments is from 2.5 to 5 mm. PET instruments have been designed with small apertures to image the brain and also with larger apertures to image the heart and other organs and tumors. Though PET is most commonly used to study the brain and the heart, whole body PET can be used to image any part of the human body. In fact the use of whole body PET to detect metastatic cancer is a rapidly growing application.[8]

(Figure 1)

Labeling Organic Compounds with Fluorine-18

General Considerations. The physical properties of the fluorine atom and the characteristics of the carbon-fluorine bond (high bond strength and similar van der Waals radius to hydrogen) also are major factors in the utility of fluorine-18 as a label for radiotracers.[9, 10] The 110 minute half life is sufficient for relatively complex synthetic manipulations and purifications and the resulting radiotracer or its labeled metabolites can be monitored in vivo for several hours. Although fluorine in chemical combination with carbon rarely occurs in nature, the development of synthetic approaches for its incorporation into organic molecules by substitution for hydrogen, hydroxyl or some other functional group often leads to organic compounds with biological properties which resemble the parent structures. The ability to substitute fluorine-18 for hydrogen while maintaining the desired biological behavior of the parent compound is well illustrated by 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}FDG, a PET tracer for 2-deoxy-D-glucose [11]) and 6-[^{18}F]fluoro-L-DOPA (a PET tracer for LDOPA[12]), two major radiotracers in PET research in the neurosciences today (Figure 2).



2-deoxy-2-[^{18}F]fluoro-D-glucose (glucose metabolism)

6-[^{18}F]fluoro-DOPA (dopamine metabolism)

Figure 2. structures of ^{18}FDG and 6-[^{18}F]fluoro-L-DOPA

Fluorine-18 Production. The short-lived positron emitters are generally produced by bombarding appropriate stable isotopes (referred to as the "target") with charged particles such as protons, deuterons, helium-3 and helium-4 traveling at high kinetic energies. These particles are most commonly and conveniently produced using a cyclotron by ionization of corresponding neutral species and are accelerated in a magnetic field which keeps the particles in a spiral track with energy being supplied to the particles by a radiofrequency source. The particles are extracted through a window in the periphery of the cyclotron and directed to impinge on a target containing the appropriate stable isotope in gas or liquid form.

Fluorine-18 production and targetry have been described in a number of publications.[5, 13] and references therein. The most commonly used nuclear reactions to produce fluorine-18, the $^{18}O(p,n)^{18}F$ and the $^{20}Ne(d,\alpha)^{18}F$ reactions, are presented in Table II. The $^{18}O(p,n)^{18}F$ reaction which yields fluorine-18 as fluoride ion is preferred in terms of yield and precursor specific activity.[14] The most common target is oxygen-18 enriched water.[15, 16] Targetry using oxygen-18 enriched carbon dioxide and oxygen gas have also been developed. The enriched carbon dioxide target produces F-18 in the chemical form of [^{18}F]fluoride ion and was developed because of the ease of recovery of enriched carbon dioxide relative to enriched water.[17] The oxygen-18 gas target was developed to produce labeled elemental fluorine taking advantage of the higher F-18 yields from the $^{18}O(p,n)^{18}F$ reaction relative to the $^{20}Ne(d,\alpha)^{18}F$ reaction.[18] The $^{20}Ne(d,\alpha)^{18}F$ nuclear reaction is most commonly carried out using neon containing 0.1% F_2 to yield ^{18}F elemental fluorine [19] which can be either used directly in synthesis or converted to other electrophilic fluorination reagents such as acetyl hypofluorite.[20, 21]

The nucleophilic and electrophilic fluorination reagents (H[^{18}F] and [^{18}F]F_2 and precursors derived from them) have been described.[3, 4, 5] In general, for equal amounts of radioactivity, the chemical mass associated with an [^{18}F]F_2 derived radiotracer (carrier-added) far exceeds that of an [^{18}F]fluoride ion derived radiotracer (no-carrier-added). Though this has been a limitation in the application of electrophilic fluorination reagents in the synthesis of F-18 labeled compounds for tracer studies where saturation, physiological and toxicological effects play important role, there has been a recent breakthrough in achieving high specific activity F-18 labeled acetyl hypofluorite using F-18 fluoride from an enriched water target. In this elegant study, ^{18}F-labeled fluoromethane ([^{18}F]CH_3F) was first prepared and subjected to an electrical discharge in the presence of unlabeled elemental fluorine (280 nmol) to yield [^{18}F]F_2 which was converted to [^{18}F]acetylhypofluorite in a specific activity of 0.35-0.6 Ci/μmol at the end of bombardment.[22] This method has been used in the radiosynthesis of 2β-carbomethoxy-3β-(4-[^{18}F]fluorophenyl)tropane ([^{18}F]CFT or WIN 35428), a cocaine analogue, for PET studies.

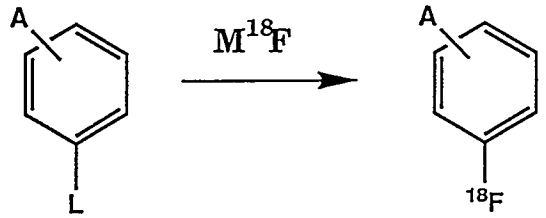
Table II. Fluorine-18 production methods.

NUCLEAR REACTION	TARGET MATERIAL	CHEMICAL FORM PRODUCED	SPECIFIC ACTIVITY	Reference
$^{18}O(p,n)^{18}F$	$H_2{}^{18}O$	[^{18}F]fluoride ion	ca. 2000 Ci/mmol	15, 16, 23
		[^{18}F]acetyl hypofluorite	350-600 Ci/mmol	22
	$C^{18}O_2$	[^{18}F]fluoride ion	ca. 2000 Ci/mmol	17
	$^{18}O_2$	[^{18}F]fluorine or [^{18}F]acetyl hypofluorite	<15 Ci/mmol	18
$^{20}Ne(d,\alpha)^{18}F$	$Ne + F_2$	[^{18}F]fluorine	<15 Ci/mmol	5, 19

Rapid Synthesis with Fluorine-18. ^{18}F-labeled aryl fluorides, aliphatic fluorides, acyl and aroyl fluorides have been synthesized using both nucleophilic and electrophilic sources of ^{18}F as labeled precursors (H[^{18}F] and [^{18}F]F_2 and precursors derived from them[3, 4, 5]). To date, the ability to produce *high specific activity* F-18 labeled compounds still remains one of the most challenging areas in F-18 synthesis. This section describes a few examples in the recent development of routes to obtain high specific activity F-18 labeled aromatic compounds.

High Specific Activity F-18 Labeled Aromatic Compounds. Over the past 25 years, many different methods have been reported for introducing ^{18}F into aromatic compounds.[5] However, to date, only the nucleophilic aromatic substitution reaction[24] satisfies the need for an efficient synthesis of aryl fluorides, especially in the case of complex molecules. The mechanism and conditions necessary for successful substitution have been the subject of a series of papers[24, 25, 26] and many F-18 labeled aromatic compounds have been synthesized using this general method.[5] and references therein

The minimal structural requirements for the nucleophilic aromatic substitution reaction are the presence of an electron withdrawing, activating substituent such as RCO, CN, NO_2 etc., as well as a leaving group, such as NO_2 or $^+NMe_3$ (Figure 3). However, there are numerous important radiotracers such as neurotransmitters and false neurotransmitters[27, 28] with electron donating substituents on the ring which can make the substitution reaction proceed in low yield or be ineffective. While these can be prepared using elemental fluorine or other electrophilic fluorination reagents, the resulting low specific activity products are a limitation with chemical compounds which are physiologically active at low administered doses. For example, F-18 labeled 6-fluorodopamine and 6-fluorometaraminol prepared from electrophilic fluorination reagents produce hemodynamic effects when administered *in vivo*.[27, 28]



A: Electron withdrawing activating group
L: Leaving group

Figure 3. Nucleophilic Aromatic Substitution Reaction with [^{18}F]Fluoride

In order to extended the utility of the nucleophilic aromatic substitution reaction to moleules containing electron donating substituents, an investigation of structure-activity relationships was carried out.[29] ^{13}C-NMR was used to probe the electron density at the ring carbon atoms of a series of aromatic nitroaldehydes with different hydroxyl protecting groups. A good correlation between the radiochemical yields for fluorine-18 substitution and the ^{13}C-NMR chemical shifts of the reaction center (where the nitro group is attached) has been demonstrated for structurally similar compounds (compounds A through F in Figure 4).[29, 30] There is a large difference in radiochemical yield between 6-nitropiperonal (compound B) and 6-nitroveratraldehyde (compound D). This appears to be associated with relatively lower electron density at the reaction center for 6-nitropiperonal as determined by the ^{13}C chemical shift. Perhaps due to the ring strain, the electron donating effect becomes less effective in 6-nitropiperonal. Application of this methodology has resulted in the first synthesis of no-carrier-added 6-[^{18}F]fluorodopamine (Figure 5), (+) and (-)-6-[^{18}F]fluoronorepinephrine and 6-[^{18}F]fluoro-L-DOPA[29, 31, 32] where the methylenedioxy moiety was used as a masked catechol which was readily removed at the end of the synthesis.

More recent developments in the synthesis of high specific activity aromatic and heteroaromatic compounds have been reported, including the reaction of F-18 fluoride with aryliodonium salts to prepare NCA aryl fluorides[33] and a study on reactivity and positional selectivity of F-18 fluoride on several substituted pyridines and diazines.[34]

(Figure 4)

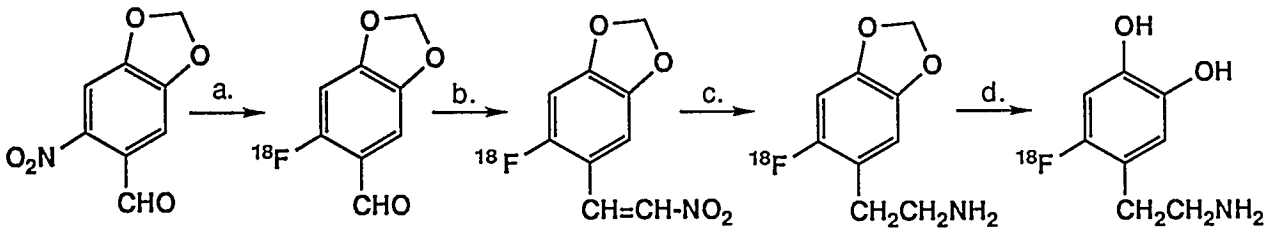


Figure 5. Synthesis of No-Carrier-Added 6-[^{18}F]Fluorodopamine. a. K^{18}F; b. CH_3NO_2; c. $LiAlH_4$; d. HI

Applications of PET Radiotracers in the Neurosciences

Once a labeling method has been established, the *in vivo* specificity of a labeled compound for a specific molecular target is determined. This is usually accomplished by studies in small animals or by *in vivo* PET studies to assess pharmacological specificity, stereoselectivity and/or kinetic isotope effects where appropriate. The extraction of quantitative physiological information usually requires the application of a kinetic model.[35,36,37]

PET, in conjunction with appropriate radiotracers, has been used to assess the functional and neurochemical parameters in the normal and diseased human brain and heart. As a result, information which could only be previously investigated in animals or in the postmortem human is accessible in human subjects. This has enabled initial investigations of the relation between the neurochemical changes in the human body and its functional and clinical consequences. Specific examples of radiotracer applications in the neurosciences (brain and heart) are given in the following sections.

Brain Glucose Metabolism. The major radiotracer for brain studies has been 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}FDG) whch was developed nearly 20 years ago and was the first radiotracer to be widely employed in PET research. ^{18}FDG measures regional brain glucose metabolism[38] in all brain regions simultaneously. Regional brain glucose metabolism reflects activity in nerve terminals and synaptic elements within it.[37] The ^{18}FDG method is based on the metabolic trapping of ^{18}FDG-6-phosphate, the product of hexokinase catalyzed phosphorylation of ^{18}FDG. Since glucose derivatives missing the hydroxyl group on C-2 do not undergo further steps in glycolysis, the radioactivity in tissue after the injection consists only of free ^{18}FDG and ^{18}FDG-6-phosphate (which remains intracellularly trapped for the time course of the measurement), allowing the measurement of glucose metabolism via a kinetic model. ^{18}FDG has become a major tool in studies of neurological and psychiatric disease[39] as well as assessing myocardial viability and tumor metabolism.[1] It has also been used to measure the effects of drugs and substances of abuse, cognitive processing and somatosensory stimulation on brain glucose metabolism. Although the ^{18}FDG method does not provide direct information on the particular neurochemical mechanism(s) involved in a disease or in drug mechanisms, the involvement of particular brain regions has been a valuable tool in understanding diseases and drug mechanisms.

Neurotransmitter Activity (Brain). A number of neurological and psychiatric disorders have been linked with abnormalities in neurotransmitter properties. The neurotransmitter systems commonly under investigation with PET include the dopamine, serotonin, opiate, benzodiazepine and cholinergic systems and F-18 labeled radiotracers which selectively bind to different synaptic elements (eg transporters, vesicles, receptors) and those which are sensitive to changes in neurotransmitter concentration have been developed.

The Dopamine System. By far, the greater effort in PET research has been directed toward the study of the brain dopamine system. This has been stimulated by the importance of dopamine in Parkinson's disease, schizophrenia and substance abuse and its vulnerability in normal aging.(for a review see[40], in press) Aspects of the dopaminergic synapse which have been studied are

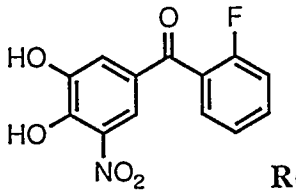
dopamine metabolism, the dopamine transporter, the dopamine D_1 and D_2 receptors,[41] vesicular storage and changes in synaptic dopamine[40] and reference therein.

Since dopamine does not cross the blood-brain barrier, the investigation of brain dopamine metabolism with PET has required a fluorine-18 labeled derivative of DOPA, 6-[^{18}F]fluoro-L-DOPA. 6-[^{18}F]Fluoro-L-DOPA has been widely used for studies of dopamine synthesis and metabolism and has been applied in clinical research in Parkinson's disease.[42, 43] 6-[^{18}F]Fluoro-DOPA crosses the blood-brain barrier and is converted to 6-[^{18}F]fluorodopamine via L-aromatic amino acid decarboxylase (AADC). It is also extensively metabolized by both monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT) in the periphery producing labeled metabolites, especially 3-*O*-methyl-6-[^{18}F]fluoro-DOPA, which contribute to striatal F-18 radioactivity as visualized by PET. Consequently, other tracers with a simpler metabolic profile have then been developed. These include [^{18}F]fluoro-*m*-tyrosine[44, 45] and β-fluoromethylene-6-[^{18}F]fluoro-*m*-tyrosine.[46] These tracers are substrates for AADC but not for COMT.

The most widely used dopamine D_2 receptor PET ligands are the ^{11}C and ^{18}F-labeled butyrophenones such as spiroperidol and its derivatives and the benzamides such as raclopride.[41 and references therein, 47, 48, 49, 50, 51]

Several radioligands have been developed to measure the dopamine transporter system for studies of addiction, normal aging and neurodegeneration.[40 and reference therein] Many of these have been labeled with carbon-11 and include [^{11}C]nomifensine, [^{11}C]cocaine and [^{11}C]*d-threo*-methylphenidate and [^{11}C]WIN 35428, a cocaine analog. F-18 labeled tracers for this system include [^{18}F]GBR 13119 and [^{11}C] and [^{18}F]WIN 35428[22] and ^{18}F-labeled cocaine analogs[52, 53]. These radioligands differ with respect to their affinities and their specificity for the dopamine transporter as well as their kinetics and the choice of the optimal radiotracer must be made in the context of its intended application.

MAO (EC 1.4.3.4) and COMT (EC 2.1.1.6) are the two major enzymes which metabolize the catecholamines, such as dopamine. Radiotracers for studying MAO have been developed though most are labeled with carbon-11.[54, 55] An exception is ^{18}F-abeled derivative of L-deprenyl which has undergone initial studies[56] and an F-18 labeled derivative of Ro19 6327 which has recently been reported.[57] The development of tracers for measuring COMT in the brain has also been undertaken, stimulated by reports of highly selective COMT inhibitor drugs having central activity. One of these is Ro41 0960, a fluorine containing nitrocatechol with a high affinity for COMT.[58] It was recently labeled with fluorine-18 using the nucleophilic aromatic substitution reaction. PET studies in baboons revealed that its brain uptake is negligible.[59] However, this unanticipated observation reveals the power of PET to examine the uptake of drugs in a living brain. This information is difficult to obtain in animals and impossible to obtain in humans by other methods.

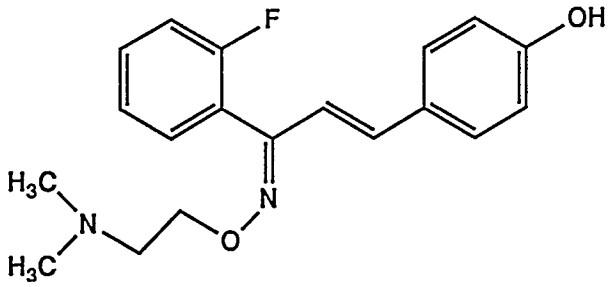


Ro41 0960 (COMT inhibitor)

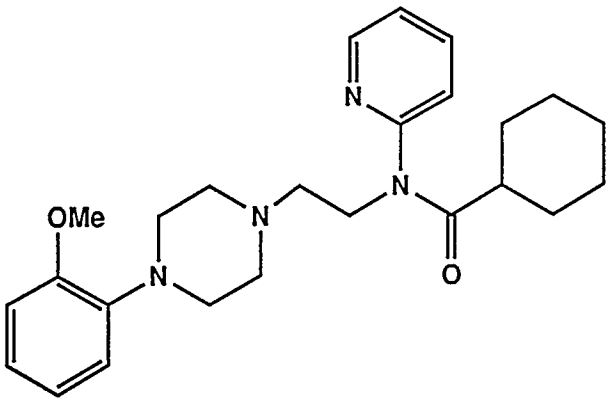
The Serotonin system. The serotonin (5-HT) system is associated with a number of neurological and psychiatric disorders and it is also an important molecular target for anti-depressant drugs.[60] Ligands to study serotonin 5-HT_2 receptors, such as [^{18}F]septoperone,[61] [^{18}F]ritanserin,[62] [^{18}F]altanserin,[63] 3-N-(2"-[^{18}F])fluoroethylspiperone,[64] and [^{18}F]fluoroethylketanserin,[65] have been prepared using the nucleophilic aromatic substitution reaction. Recently, a highly potent and selective 5HT_2 receptor antagonist SR 46349B has been labeled with ^{11}C and ^{18}F to study the interactions between neurotransmitter systems.[66, 67] Derivatives of N-phenethylpiperinine have also been labeled and are under evaluation.[68, 69, 70, 71]

The mechanism of action of some antidepressant drug is believed to involve adaptive changes in central serotonin 5-HT_{1A} receptors. Therefore, the development of radiotracers for serotonin 5-HT_{1A} receptors has received considerable attention. Although much effort has been focused on ^{11}C (e.g., a selective antagonist [^{11}C]WAY 100635[72, 73]), the development of ^{18}F derivatives are also underway.[74]

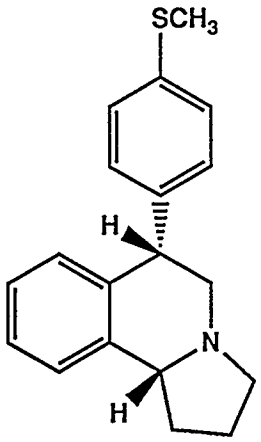
The development of serotonin transporter imaging agents has also been of great interest in order to study the role of this regulatory site in a variety of psychiatric, psychomotor and addictive disorders.[75] Citalopram,[76] paroxetine,[77] fluoxetine,[78] and nitroquipazine,[79] potent serotonin transporter ligands, have been radiolabeled with carbon-11 or fluorine-18 for evaluation as radiotracers for imaging and quantifying serotoinin transporter sites in the brain using PET. Recently, a potent serotonin transporter inhibitor, trans-1,2,3,5,6,10β-hexahydro-[4-(methylthio)phenyl]pyrrolo[2,1-α]isoquinoline (McN-5652Z), has been labeled with C-11[80] and a fluoroethylthio analogue of this pyrroloisoquinoline derivative has been also labeled with F-18 for evaluation as a potential PET serotonin transporter ligand.[81, 82]



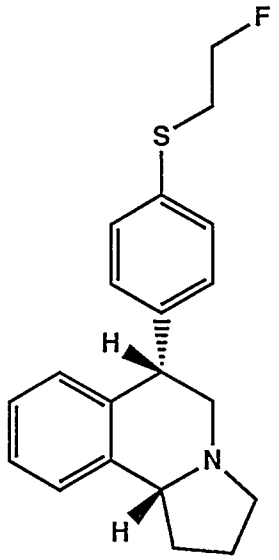
SR 46349B
(5HT_2 antagonist)



WAY 100635
(5-HT_{1A} antagonist)

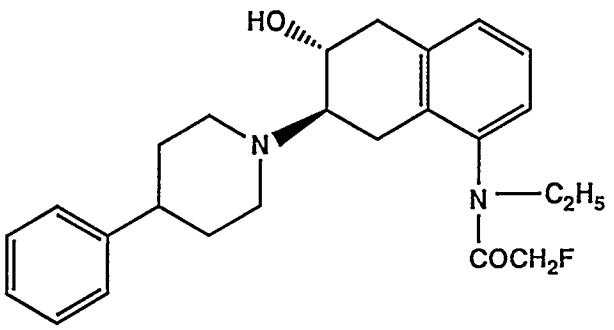


McN-5652Z



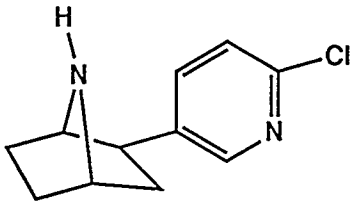
Fluoroethylthio-McN-5652Z
(serotonin transporter inhibitors)

The Cholinergic System. The characterization of the cholinergic system *in vivo* is of interest because of its role in memory and its involvement in Alzheimer's disease. Radiotracer development in this area has focussed on Alzheimer's disease with a view to presymptomatic detection of degenerative processes and for monitoring drug therapy. Two major structural classes of compounds, the benzovesamicols and trozamicols, have been developed and radiolabeled to map the cholinergic neurons[83, 84, 85, 86] based on the rationale that these high affinity ligands can selectively bind to vesicular receptors which are uniquely situated on the cholinergic synaptic vesicles.[87] One of these is [^{18}F](-)-4-N-ethyl-fluoroacetamidobenzovesamicol.[88]



(-)-4-N-ethyl-fluoroacetamidobenzovesamicol (cholinergic vesicular receptor ligand)

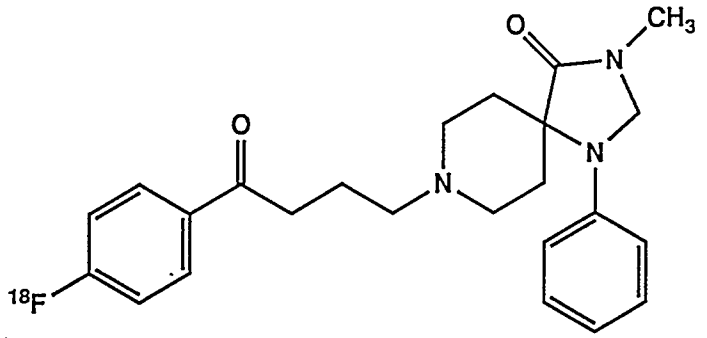
Radiotracers for postsynaptic cholinergic receptors have also been developed. For example, F-18 labeled fluoroalkyl derivatives of quinuclidinyl benzilate are under investigation as subtype selective muscarinic ligands.[89] 2- and 4-[^{18}F]Fluorodextetimide also have been developed to study muscarinic-cholinergic receptors.[90, 91] Recently, fluorine-18 labeled analogue of epibatidine has been developed to study nicotinic-cholinergic receptors.[92]



(±) Epibatidine (nicotinic receptor agonist)

The Opioid System. The opioid system has been implicated in a number of neurolgical and psychiatric conditions including pain, addiction and seizure disorders. F-18 labeled opiate receptor ligands, such as 6β-fluorocyclofoxy,[93] fluoroalkyl derivatives of diprenorphrine and buprenorphrine[93, 94, 95, 96] and derivatives of fentanyl,[97] have been developed for application in PET studies.

Neurotransmitter Interactions. Though many radiotracers have been developed to selectively probe discrete neurotransmitter systems in vivo with PET, it is well known that different neurotransmitters also interact with one another. These interactions provide for a fine degree of control over neuronal activity. Recently, studies have also been designed to probe neurotransmitter interactions with PET; for example, to evaluate the ability of acetylcholine,[98, 99, 100] GABA,[101] serotonin,[102] and opiate systems[103] to modulate striatal dopamine release using dopamine D_2 ligand [^{18}F]N-methylspiroperidol or [^{11}C]raclopride. In human, the interactions between dopamine and acetylcholine have been investigated in healthy normal subjects.[104] Striatal dopamine D_2 receptors and acetylcholine interactions have also been studied in primates using [^{18}F](-)-4-N-ethyl-fluoroacetamidobenzovesamicol as a radioligand marking cholinergic activity.[88]



[^{18}F]N-methylspiroperidol (dopamine D_2 ligand)

Neurotransmitter Activity (Heart). (-)-Norepinephrine is the major neurotransmitter of the sympathetic nervous system. It is synthesized and stored within the cardiac sympathetic neuron and released in response to nerve impulses. The major mechanism for terminating the action of released (-)-norepinephrine is reuptake via the norepinephrine transporter (uptake 1) and storage within the cardiac neuron. Dysfunction in this system may underlie a number of cardiac diseases and may also play a role in the cardiotoxicity of psychostimulant drugs such as cocaine.

Radiotracers have been developed to study cardiac sympathetic activity *in vivo*. These include false neurotransmitters labeled with carbon-11 ([^{11}C]hydroxyephedrine[105]) and with fluorine-18 ([^{18}F]metaraminol[106]) as well as the simple fluorine substituted derivatives of norepinephrine, (-)-and (+)-6-[^{18}F] fluoronorepinephrine ((-) and (+)-6-[^{18}F]FNE [107]) along with 6-[^{18}F]fluorodopamine (6-[^{18}F]FDA,[27, 108] which is converted to (-)-6-[^{18}F]FNE *in vivo* [109]).

Mechanistic studies employing deuterium isotope effect have been carried out to understand the behavior of 6-[^{18}F]FDA *in vivo*, in particular its uptake and rapid clearance from the heart which differs from (-)-6-[^{18}F]FNE which has a very slow clearance rate. In the metabolism of the parent compound, dopamine, MAO catalyzes the cleavage of the C-H bond alpha to the amino group[110] and DBH (dopamine β-hydroxylase) cleaves the benzylic C-H bond leading to the formation of (-)-norepinephrine[111, 112] In order to selectively probe the contribution of these two metabolic enzymes to the kinetics of 6-[^{18}F]fluorodopamine *in vivo* (Figure 6), doubly labeled (fluorine-18 and deuterium) isotopomers of 6-[^{18}F]fluorodopamine were synthesized and used in PET studies[113, 114] The kinetics of the parent radiotracer and the deuterium substituted derivatives were compared using PET in baboons. The clearance rate of F-18 from the heart was reduced by deuterium substitution in the α position to the amino group but not the β-position indicating that MAO catalyzed oxidation is responsible for the rapid clearance of F-18 from the heart after the injection of 6-[^{18}F]FDA (Figure 7). This study demonstrates that deuterium substitution is an effective mechanistic tool allowing the identification of the specific chemical transformation contributing to a PET image *in vivo* without tissue sampling and without pharmacological intervention.

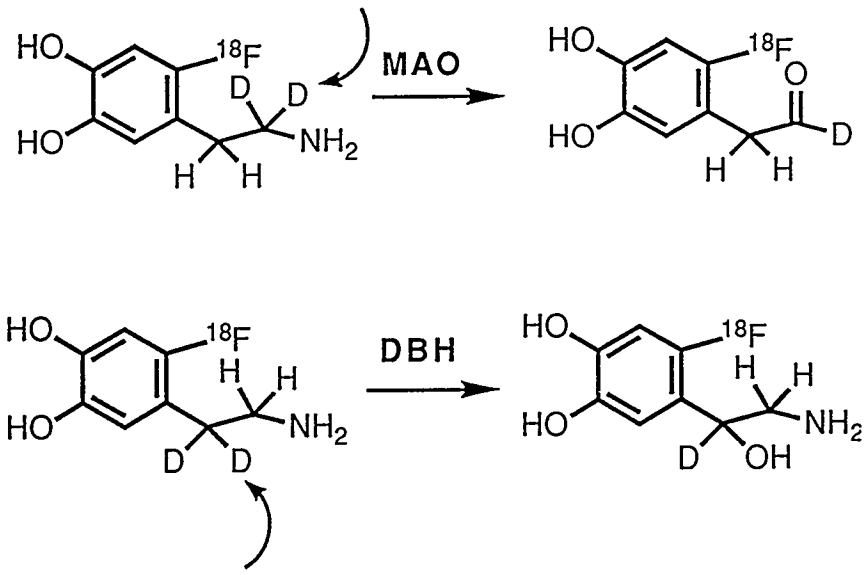


Figure 6. Specifically deuterated 6-[^{18}F]FDA derivatives for probing MAO and DBH.

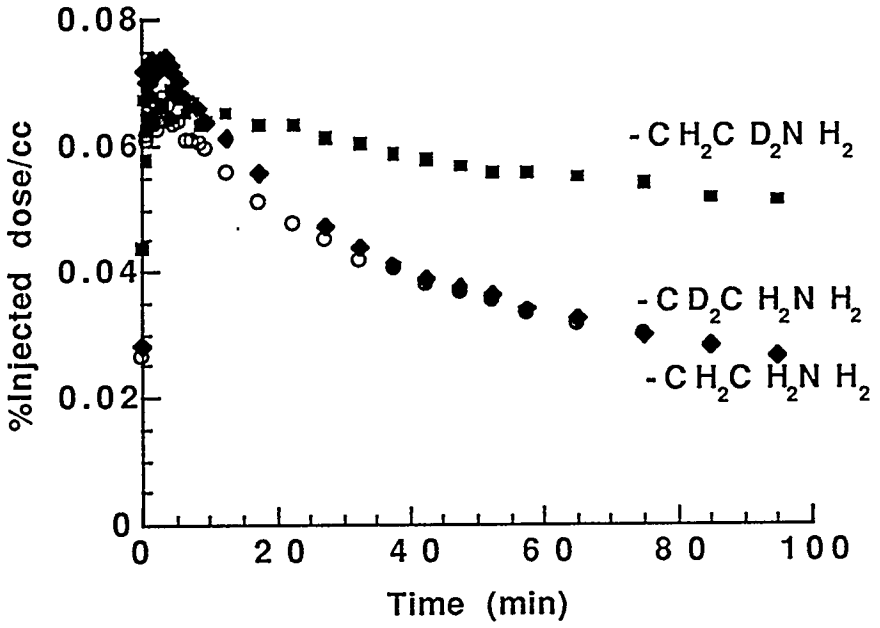


Figure 7. Uptake and clearance of ^{18}F after injection of 6-[^{18}F]FDA (open circles) and 6-[^{18}F]FDA-α,α-D_2 (squares), and 6-[^{18}F]FDA-β,β-D_2 (diamonds) in baboon heart.

PET and F-18 Tracers in Neuropharmacology

PET has become an important scientific tool for examining the behavioral, therapeutic and toxic properties of drugs and substances of abuse[115] PET provides a new perspective on drug research because it can assess both pharmacokinetic and pharmacodynamic aspects of drug action directly in the human body both in normal controls and in patients. The ability to assess the behavior of a drug at its site of action directly in human subjects is important because the behavior of a drug may vary across animal species and even between different categories of human subjects where it can be affected by age, gender, disease, drug status and other factors. PET also enables the assessment of drug behavior in diseases where there are no animal models. This information places PET in a unique position to characterize drug binding sites and to understand the molecular mechanisms underlying drug action.

The pharmacokinetics of a drug can be monitored with F-18, providing that the drug is a fluorine containing compound and is amenable to labeling with fluorine-18. There are a number of examples of fluorine-containing drugs which have been labeled with fluorine-18 includng the antipsychotic drugs haloperidol[116] and BMY 14802[117] Fluorine-containing anesthetics have also been labeled with F-18 and their distribution and kinetics studied in the human brain.[118] These studies are most often undertaken to determine the amount of drug which reaches its target organ as well as to better understand drug mechanisms.

While drug pharmacokinetics can be measured using the labeled drug, the effects of the drug on the body (pharmacodynamics) can be measured using radiotracers which have specificity for a discrete biological process such as metabolism, neurotransmitter activity, blood flow, enzyme activity or other processes. For example, PET studies of the effects of chronic cocaine use on the human brain with both ^{18}FDG (which measures brain glucose metabolism) and [^{18}F]N-methylspiroperidol (which measures dopamine D_2 receptor availability), have revealed that cocaine abusers have decreased dopamine D_2 receptor availability and that there is a significant correlation between decreased dopamine D_2 receptor availability and metabolism in frontal areas.[40] This has led to the suggestion that dopamine dysregulation may be responsible for the loss of control and compulsive drug taking behavior seen in the cocaine abuser. Another study using (-)-6-[^{18}F]fluoronorepinephrine to assess the functional activity of the norepinephrine transporter in the heart revealed that an acute dose of cocaine disables the uptake 1 mechanism.[119] This mechanism may play a role in the cardiotoxicity of cocaine.

PET has also been used to examine the pharmacokinetics and pharmacodynamics of the widely used antipsychotic drug, haloperidol.[116, 120, 121, 122] In these studies, labeled haloperidol was used to assess the distribution and kinetics of the drug in the brain and [^{18}F]N-methylspiroperidol was used to assess the time course of occupancy of dopamine D_2 receptors by haloperidol[121] and the relationship between plasma drug levels and receptor occupancy.[123] These studies showed that increasing the dose of haloperidol does not result in increased receptor occupancy, consequently, promoting the use of lower doses of antipsychotic medication in the treatment of patients with psychotic disorders.

In another study, an F-18 labeled derivative of captopril, an angiotensin converting enzyme (ACE) inhibitor used to treat hypertension, was used to examine the behavior of a series of ACE drugs.[124]

Summary and Outlook

Though the major focus of this chapter was on fluorine-18 labeled radiotracers, there is a strong synergism between the radiotracer development with fluorine-18 and radiotracer development with carbon-11. Thus a well-balanced perspective of the field requires the consideration of progress with each of these isotopes. Within this context, it is important to emphasize the essential and pivotal role that organic synthesis has played in the progression of the PET field over the past twenty years from one in which only a handful of institutions possessed the instrumentation and staff to carry out research to the present-day situation where there are more than 200 PET centers worldwide. During this period PET has become an important scientific tool in the neurosciences, cardiology and oncology.

It is important to point out that PET is by no means a mature field. The fact that a hundreds of different F-18 labeled compounds have been developed but only a few possess the necessary selectivity and sensitivity *in vivo* to track a specific biochemical process illustrates this and underscores a major difficulty in radiotracer development, namely the selection of priority structures for synthesis and the complexities of the interactions between chemical compounds and living systems.

New developments in rapid organic synthesis are needed in order to investigate new molecular targets and to improve the quantitative nature of PET experiments. Though PET is a challenging and expensive technology, it is exquisitely suited to human studies, particularly to studies of the functional and neurochemical organization of the normal human brain and other organs and to delineating mechanisms underlying neurological and psychiatric disorders. It also provides uniquely useful clinical information relative to the management of brain tumors, epilepsy and heart disease. Its use in drug research and development holds promise in understanding drug action, in facilitating drug discovery and in the introduction of new drugs into the practice of medicine. A new challenge is also present with the advent of functional magnetic resonance imaging (fMRI) and new strategies are being developed for synergistic imaging in which the data from both image modalities is fused to generate an image that has the spatial resolution of MRI with the biochemical information from PET.

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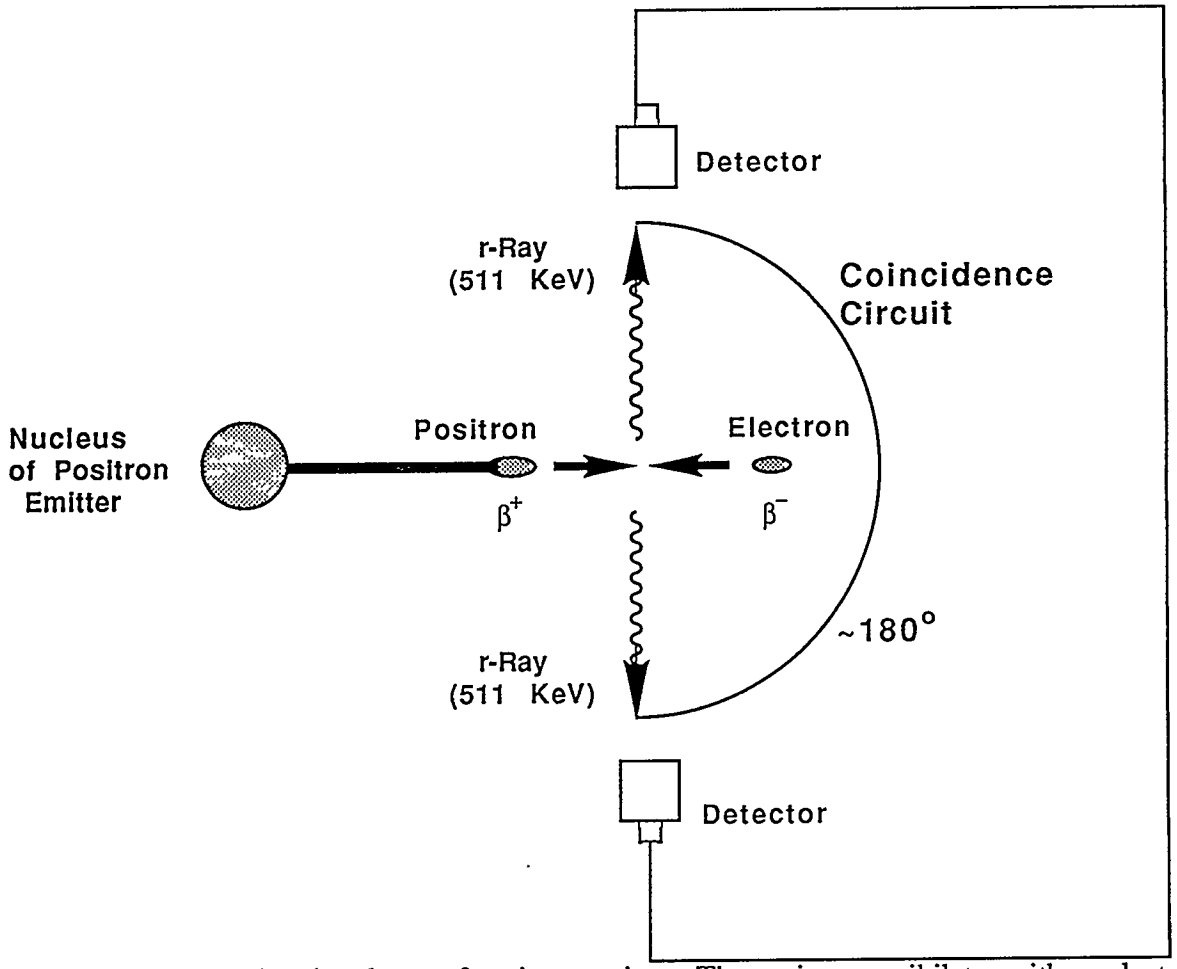

Figure 1 Diagram showing decay of positron emitter. The positron annihilates with an electron generating two 511 KeV r-rays at ca. 180° which penetrate the body barrier and are detected by coincidence detection.

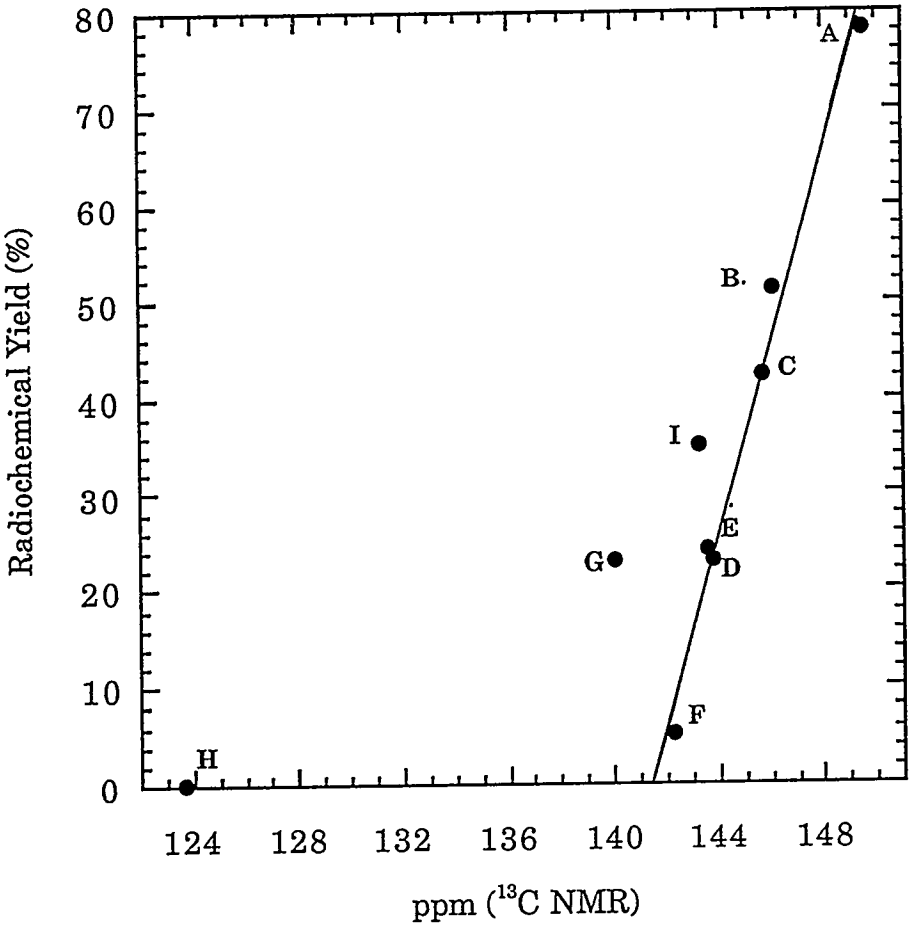

Figure 4. Correlation between the ^{13}C chemical shift of the reaction center and the radiochemical yield.

A. 2-nitrobenzaldehyde; B. 6-nitropiperonal; C. 3,4-O-isopropylidene-benzaldehyde; D. 6-nitroveratraldehyde; E. 3,4-dibenzoxy-6-nitrobenzaldehyde; F. 2-nitro-5-methoxybenzaldehyde; G. 2-nitro-3-methoxybenzaldehyde; H. 1,4-benzodioxan-6-carboxyaldehyde; I. 3-methoxy-4-nitrobenzaldehyde. (Data from reference[29]).