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The Heritage of Radiotracers for PET

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Abstract

The history of PET research clearly demonstrates that it is advances in chemistry coupled with a detailed examination of the biochemistry of new radiotracers which has allowed the PET method to be applied to new areas of biology and medicine. Radiotracers whose regional distribution reflects glucose metabolism, neurotransmitter activity and enzyme activity have all required the development of rapid synthetic methods for the radiotracers themselves and the characterization of their biochemical behavior. This article traces some of the advances in the production of labeled precursors and in radiotracer synthesis and evaluation which have shaped the rapidly expanding application of PET to problems in the neurosciences, in cardiology and in oncology.

Carbon-11 and fluorine-18, the most commonly used radiotracers for PET, were discovered more than 50 years ago. The discovery of carbon-11 actually preceded that of carbon-14 so it, in fact, provided the first opportunity to trace carbon.[30] In his autobiography, Martin Kamen, the co-discoverer of carbon-14, describes the early trials of using carbon-11 to study photosynthesis and the metabolism of simple carbon compounds.[29] Kamen's recounts of the research which took place were dominated both by the excitment and by the problems and frustrations of working with this 20 minute half life isotope. Despite this initial interest in carbon-11, its use in research was soon supplanted by the long-lived carbon-14 which was discovered several years later and was far more convenient to use.

Interest in carbon-11 and the other short lived positron emitters was renewed in the mid-1960's fueled by advances in chemistry and in PET instrumentation. The development of in vivo tracer methods such as oxygen-15 tracers for measuring regional blood flow, blood volume and oxygen extraction[47] and the carbon-14 autoradiographic method for determining regional brain glucose metabolism in animals[46] (later extended to humans through the development of 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}FDG)) [40] all played an important role in the emerging development of quantitative PET methods.

The purpose of this article is to trace some of the milestones in the chemistry related to the development of radiotracers for PET and to give a few examples of the diverse problems which are currently being addressed by the PET method. Positron emitter labeled radiotracers and other topics related to PET are also covered comprehensively in a recent text[18] and in a recent article.[52]

The Cyclotron Production of Carbon-11 and Fluorine-18

The short lived positron emitters carbon-11, fluorine-18, nitrogen-13 and oxygen-15 are typically produced on a cyclotron. Alternatively, radionuclide generators for producing rubidium-82m and gallium-68 are commercially available. However, the majority of the radiotracers which are used in PET research today are labeled with carbon-11 or with fluorine-18. The production of carbon-11 and fluorine-18 in high yield, in high specific activity and in useful chemical form challenged chemists even before PET came on the scene. Indeed many of the gold standard methods for radionuclide production and radiotracer synthesis had their roots in fundamental research in hot atom chemistry or in mechanistic organic chemistry.[53]

Carbon-11: Carbon-11 (as $^{11}CO_2$) was first produced on a cyclotron by bombarding boric oxide with deuterons while maintaining the target material at its melting point to release the radioactive gas.[11] These targets were not convenient to use and there was little control over the chemical form of carbon which was obtained from the target. A breakthrough in carbon-11 production was realized when high yield nitrogen gas targets were developed making it possible to control the chemistry which occurred in the target and to produce useful labeled precursors such as carbon dioxide and hydrogen cyanide.[10] Thus boric oxide targets became obsolete except in institutions having a single particle (deuteron) cyclotron. Nitrogen gas targets based on these early designs are now used in virtually every PET center throughtout the world for producing high specific activity carbon-11 labeled precursors required for the synthesis of complex radiotracers for PET. With the increasing application of PET in the clinical setting and the establishment of a number of clinical PET centers where a small medical cyclotron is installed in a hospital setting, these gas targets have proven to provide the reliable

and routine delivery of carbon-11 required for the transfer of many of the breakthroughs in basic radiotracer research to the clinical setting.

Fluorine-18: The first fluorine-18 labeled precursor molecule for radiotracer synthesis was [^{18}F]fluoride ion[39] and its production from water targets ($H_2{}^{16}O$) bombarded with alpha particles or helium-3 was described over 20 years ago.[12] The widespread use of small medical cyclotrons and the demand for fluorine-18 as a label for radiotracers required a method for its production in high yield from relatively low energy protons. Measurement of the absolute cross section for the $^{18}O(p,n)^{18}F$ reaction[41] demonstrated the advantage of this reaction and miniaturized water ($H_2{}^{18}O$) targets were then developed.[51,31] The enriched water target technology represented a necessary breakthrough in the routine, reliable production of fluorine-18 on small medical cyclotrons and today small volume enriched water targets are in routine use at most PET centers providing high specific activity fluorine-18 (as fluoride) for the synthesis of radiotracers such as ^{18}FDG.

Although [^{18}F]fluoride generally produced with enriched water targets is now the basis for the synthesis of ^{18}FDG[25] and the ^{18}F-labeled neurotransmitter and steroid hormone receptor ligands,[32] the first synthesis of ^{18}FDG used [^{18}F]F_2 and required the development of cyclotron targetry for producing fluorine-18 labeled elemental fluorine as well as an investigation of the suitability of this highly reactive halogen as a reagent for radiotracer synthesis.[35,20,26] The development of reliable targets for producing [^{18}F]F_2 was based on a detailed investigation of target materials which would withstand the highly reactive fluorine gas and would yield the proper chemical form of fluorine-18 for radiotracer synthesis.[6,8] [^{18}F]F_2 has since been used as a source of other labeled electrophilic fluorination

reagents such as acetyl hypo[^{18}F]fluorite which has an advantage over elemental fluorine in certain radiotracer syntheses.[1,43]

Radiotracers Labeled with Carbon-11 and Fluorine-18

Although literally hundreds of different chemical compounds labeled with carbon and fluorine-18 have been reported,[18] only a dozen or so have been widely applied in PET research today. This reflects the difficulty in designing radiotracers whose concentration in tissue represents an identifiable biochemical process and the fact that many labeled compounds were developed without considering their ultimate use as tracers. The dozen or so carbon-11 and fluorine-18 labeled compounds include amino acids, sugars, fatty acids, biogenic amines, receptor active compounds and therapeutic drugs to name a few. They are currently being used in basic and clinical research for probing the biochemical transformations accompanying normal function as well as the biochemical abnormalities underlying tumor development, neurological and psychiatric ilnesses such as Parkinson's disease and schizophrenia and Alzheimer's disease and heart disease. PET is also finding increasing use as a method for identifying drug binding sites[21], receptor occupancy by drugs[45], and the effect of route of administration on drug disposition.[49]

The development of ^{18}FDG in 1976 was a major stimulus for the growth of the PET field.[17] ^{18}FDG is now produced routinely in virtually every PET center in the world and is still the most widely used radiotracer in PET research. With major applications in psychiatry, neurology, oncology and cardiology, it promises to play a major role in the emerging clinical PET centers. It is noteworthy that optimizing the synthesis of ^{18}FDG has challenged chemists for more than a decade[17] and that this has resulted in the development of a simple, high yield synthesis amenable to automation.[25]

The study of neurotransmitters was also one of the early goals for PET and the first radiotracer to be developed for studying brain dopamine was [^{18}F]fluoroDOPA.[15] The evolution of the synthesis of 6-[^{18}F]fluoro-L-DOPA from a Sciemann reaction[16] based synthesis to an electrophilic [^{18}F]fluorodemercuration reaction[37] exemplifies the evolution of synthetic methodology to meet the demands for a particular radiotracer. In a recent development the fluorodemercuration has also been applied to the synthesis of [^{18}F]fluorometaraminol, a radiotracer for mapping adrenergic neurons in the heart.[38]

Although fluorine-18 labled dopamine receptor antagonists were also target tracers, the lack of synthetic methodology for introducing fluorine-18 in sufficiently high yield and high specific activity proved to be an initial obstacle in the exploitation of this class of tracers. Early methods of fluorination such as the Schiemann reaction were used to label the butyrophenone antipsychotic drug haloperidol with fluorine-18, but at very low specific activity.[34] Later the triazene decomposition was also applied to the synthesis of butyrophenones, and although the specific activities were very high, the yields were too low to be practical.[48] A breakthrough occurred when research on the nucleophilic aromatic substitution reactions of fluoride ion paved the way for the synthesis of fluorine-18 labeled neurotransmitter receptor ligands in sufficiently high yield and high specific activity for PET studies of the dopamine receptor in the living brain.[35] A later important development was the observation that kryptofix 2.2.2 significantly increased the reactivity of [^{18}F]fluoride.[25]

Promising new radiotracers for PET whose synthesis is based on nucleophilic aliphatic or aromatic substitution with [^{18}F]fluoride include the hypoxic cell sensitizer [^{18}F]fluoromisonidazole,[27] the S_2 antagonist

[^{18}F]setoperone,[13] the dopamine uptake antagonist [^{18}F]GBR 13119,[33] and [^{18}F]fluoroestradiol for imaging hormone dependent breast tumors.[7]

Even though the nucleophilic aromatic substitution reaction is the basis for the synthesis of many high specific activity receptor active tracers, there is still a great need for improving this reaction and for the continued development of new synthetic strategies based on high specific activity [^{18}F]fluoride. For example, presently it is difficult to synthesize a no-carrier-added fluorine-18 labeled aryl fluoride which does not possess an electron withdrawing group on the aromatic ring even though there are many interesting molecules which contain aromatic rings which are not deactivated. For complex molecules such as [^{18}F]N-methylspiroperidol,[44] the nucleophilic aromatic substitution still either requires a multistep synthesis or extensive purification of product and does not approach the synthetic simplicity of carbon-11 labeled methyl iodide based radiotracers.[36] Nonetheless, fluorine-18 does have an advantage over carbon-11 with its longer half life and the possibility of measuring the temporal concentration of radioactivity over several hours and obtaining important kinetic parameters.[4] With the carbon-11 and fluorine-18 labeled receptor active radiotracers, it is now possible test the importance of a number of medical hypotheses concerning the biochemical basis of neurological and psychiatric disease as well the mechanism of action of certain antipsychotic drugs.

Because of the early problems in labeling radiotracers with fluorine-18 in high specific activity, the early PET studies of the dopamine receptor in baboons and humans used carbon-11 labeled tracers.[18,50] In fact the carbon-11 labeled compounds continue to play a prominent role in the PET studies of neurotransmitter receptors especially with carbon-11 methyl iodide based radiotracers such as N-[^{11}C-methyl]spiroperidol[50] and [^{11}C]nomefensine,[2]

[^{11}C]carfentanyl[28] and [^{11}C]diprenorphine [28] and N-[^{11}C-methyl]-bromo-LSD[54] for PET studies of the dopamine receptor and the dopamine transport system, the opiate receptor and the serotonin (S_2) receptor. New carbon-11 labeled compounds are also being applied to receptor studies of the heart.[9] Carbon-11 labeled radiotracers play a special role in PET because, unlike fluorine-18, they offer the potential of labeling any organic molecule by isotopic substitution without changing the properties of the parent molecule. They also offer the possibliity of serial PET studies at short time intervals.

Mechanistic Studies Related to Radiotracer Development

The basis for the use of PET to obtain quantitative information on biochemical transformations in the living body resides in an identification of the factors which are responsible for the uptake and retention of radioactivity in tissue. For example, the development of the 2-deoxy-2[^{18}F]fluoro-D-glucose method was accompanied by a demonstration that metabolic trapping of the ^{18}FDG-6-phosphate was responsible for the concentration of tracer in tissues such as brain and heart.[24] More recently, the principle of metabolic trapping has been applied to the in vivo labeling of monoamine oxidase (MAO) in human brain using carbon-11 labeled suicide enzyme inactivators [21,42] and this approach has also been used to measure the rate of monoamine oxidase synthesis in baboon brain.[3] This particular study has included the use of stereoselectivity, deuterium isotope effects and pharmacological profile to characterize the uptake and retention of carbon-11 in tissue at the molecular level and to identify the specific bond which is broken in the rate limiting step.[22]

Summary

Advances in the chemical sciences and their application to the development and understanding of new radiotracers have been the major driving

force responsible for shaping the state of the art in PET research as we know it today. We feel that it is safe to say that the vitality and evolution of the PET field and the development and application of the new methods and new technologies to problems in the basic and clinical research arenas will continue to be shaped, in large part, through innovation in chemistry and through the application of chemical probes to the development of highly selective radiotracers for PET.

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