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SHORT-LIVED POSITRON EMITTER LABELED RADIOTRACERS - PRESENT STATUS

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Widespread interest in the application of positron emission transaxial tomography (PETT) and organic molecules labeled with short-lived positron (β^+) emitting nuclides to the study of physiological processes in the living human body (1,2,3) has been brought about largely by the demonstration that one of the elegant methods of neurochemical autoradiography (4), namely the ^{14}C -2-deoxyglucose (^{14}C -2DG) method (5), could be extended to humans by using these techniques. For example, by using 2-deoxy-2 [^{18}F]fluoro-D-glucose (^{18}F FDG), a β^+ emitter labeled analog of 2DG, it has been possible to correlate regional brain glucose metabolism with functional activity in humans during normal circumstances (6-8), under conditions of somatosensory stimulation (9-12) and in psychiatric conditions (13-16). This characterization of the metabolic activity of the functioning human brain and other organs such as the heart (17) depends on the use of positron emission transaxial tomography (PETT), a method of detection which gives an image of the distribution of the labeled tracer in a transverse section of the body (18-22) allowing the quantitation of radioactivity in a discrete volume of tissue. By applying PETT, the appropriate labeled tracers and mathematical models (3) to problems in the biomedical sciences it has been possible for the first time to obtain regional metabolic information in the living human body at little or no risk. Such studies are truly multidisciplinary and require a coordination of efforts in cyclotron (accelerator) technology, nuclide and labeled compound preparation, PETT and computer science and research in biology and medicine. Today, many coordinated cyclotron-PETT centers, dedicated solely to applying this powerful new technique to a variety of problems, are emerging.

This chapter will describe some of the problems and progress in the synthesis of short-lived β^+ emitter (^{11}C , ^{18}F , ^{13}N) labeled tracers for PETT within the context of their application to problems in the biomedical sciences. For a comprehensive treatment of the subject of rapid synthesis of organic molecules labeled with carbon-11, fluorine-18 and nitrogen-13 the reader is referred to a recent monograph on the subject (23).

Research in Rapid Organic Synthesis

The challenge associated with developing a synthetic strategy within the constraints of time, a limited number of precursors, and micro-scale experimental setup, where the final product must be suitable for injection into humans, are ones that are attracting a growing number of organic chemists. While research in rapid labeling is most easily accomplished at institutions with dedicated cyclotron-PETT programs, it has also been undertaken at institutions which have no access to accelerators or imaging equipment and at new institutions which are not yet completely equipped.

The numbers of institutions (including those in various stages of development) which have programs devoted to research in rapid labeling of organic molecules for application in PETT total 44 worldwide with the breakdown being 24 in North America, 10 in Europe, 1 in the Middle East and 9 in the Far East. The fact that many of these are new, attests to the widespread interest and growth of the field.

Properties of the Positron-Emitters

Carbon-14 and tritium play a special role in the study of biochemical processes because they can be substituted for stable carbon and hydrogen in organic molecules without significantly altering the properties of these molecules. Similar substitutions can also be made with ^{11}C , ^{13}N , ^{15}O and to some extent ^{18}F to give another class of radiotracers which add a new dimension and potential to the application of radiotracer methods in human studies. The positron emitters decay to produce two 511 KeV photons which, unlike carbon-14 and tritium, penetrate and can be detected externally to the body barrier. Furthermore, their short half life makes them safe from the standpoint of radiation dosimetry and their potentially high specific activity makes it possible for them to be used as labels for relatively toxic substances where the resulting tracers show no physiological effects. The complementarity of ^{14}C and ^3H on one hand and ^{11}C , ^{18}F , ^{13}N and ^{15}O , on the other is well illustrated by the current efforts in extending a number of methods in neurochemical autoradiography (4) to human studies with PETT. The physical properties of tritium, carbon-14, carbon-11, nitrogen-13 and fluorine-18 are shown in Table 1. Three properties, the short half-life, decay by body penetrating radiation and potentially high specific activity are responsible for the unique problems in the development of practical synthetic strategies to radiotracers labeled with β^+ emitters.

Table 1. Physical Properties of Tritium, Carbon-14, Carbon-11, Nitrogen-13 and Fluorine-18

Nuclide	Half-life	Decay Mode	Maximum Energy (MeV)	Range ^a mm (H ₂ O)	Maximum Specific Activity (Ci/mol)
Tritium	12.35y	β ⁻ (100%)	0.0186	0.0072	2.90 x 10 ⁴
Carbon-14	5730y	β ⁻ (100%)	0.155	0.359	62.4
Carbon-11	20.3m	β ⁺ (99+%)	0.96	4.108	9.22 x 10 ⁹
Nitrogen-13	9.96m	β ⁺ (100%)	1.19	5.39	1.89 x 10 ¹⁰
Fluorine-18	109.7m	β ⁺ (97%) EC(3%)	0.635	2.39	1.71 x 10 ⁹

^a Maximum.

Labeled Precursors for Radiotracer Synthesis

Table 2 gives a listing of some of the simple ¹¹C, ¹⁸F and ¹³N labeled compounds which are available for organic synthesis. A comprehensive listing of precursors can be found elsewhere (23). In terms of simplicity and ultimate application in humans, the most attractive synthetic strategies are those which use precursors which are available either directly from the target or through some "on-line" process which does not involve wet chemical techniques. The conversions of these precursors to other labeling reagents which may be required for a particular organic synthesis requires time and increases the complexity of an experimental setup. For example, ¹¹CO, ¹¹CO₂ and H¹¹CN are

Table 2. Some simple β⁺ emitter Labeled Compounds for Synthesis

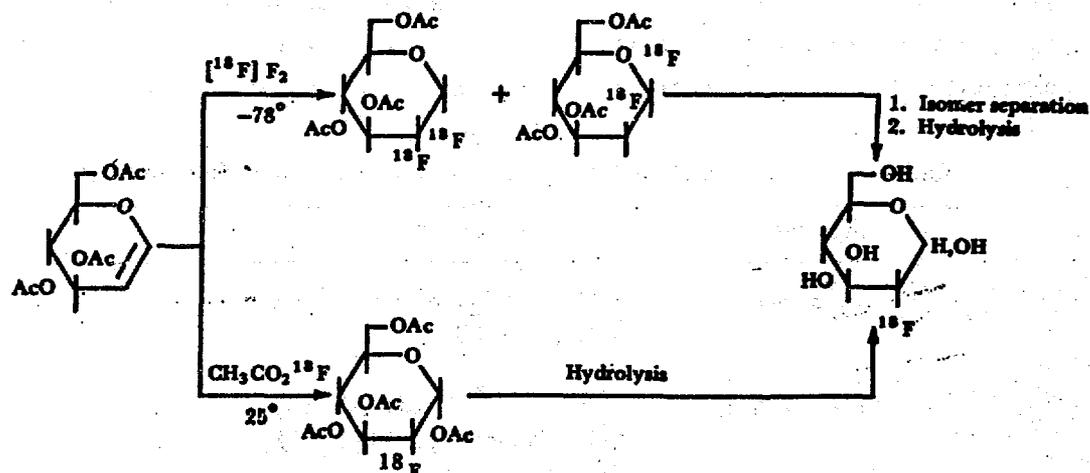
Isotope	Precursor
Carbon-11	¹¹ CO, ¹¹ CO ₂ , H ¹¹ CN, H ¹¹ CHO ¹¹ CH ₃ I, ¹¹ COCλ ₂
Fluorine-18	[¹⁸ F]F ₂ , H ¹⁸ F (anhydrous) H ¹⁸ F (aqueous), CH ₃ CO ₂ ¹⁸ F, CλO ₃ ¹⁸ F
Nitrogen-13	¹³ NH ₃ , ¹³ NO ₂ ⁻ , ¹³ NO ₃ ⁻

available directly whereas H¹¹CHO and ¹¹COCλ₂ require a more complex experimental setup (23,24).

LABELED COMPOUNDS FOR PETT

The incentive for developing rapid routes to various classes of compounds often originates with the desire to extend a particular neurochemical autoradiographic technique to humans. Three such examples are the study of regional brain glucose metabolism, the study of brain protein metabolism and the study of neurotransmitter receptors. Examples of the synthetic efforts made in each of these areas are summarized below.

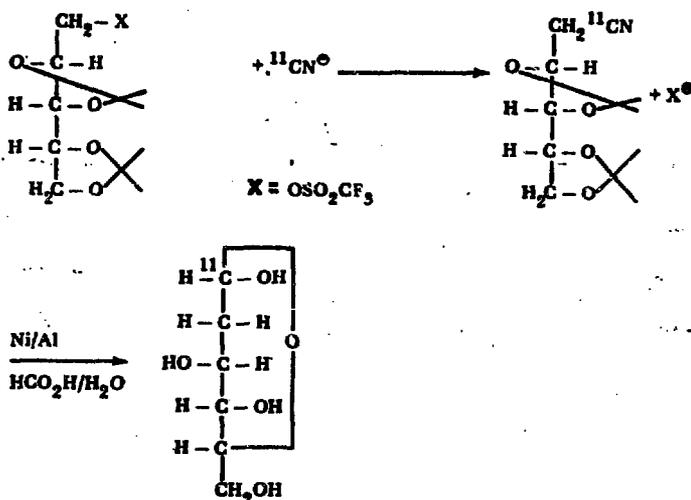
Labeled Sugars: The measurement of regional brain glucose metabolism in animals using ^{14}C -2DG and autoradiography is a technique which has been applied to a wide variety of problems in the neurosciences (5). Several years ago this method was first applied to humans using 2-deoxy-2- ^{18}F fluoro-D-glucose (^{18}F FDG) and PETT (25). Unlabeled 2-deoxy-2-fluoro-D-glucose had previously been shown to have similar properties to 2-deoxy-D-glucose in that it was a good substrate for hexokinase (26) and would be predicted to undergo facilitated transport into the brain. This information supported the contention that F for H substitution at C-2 would produce an analog which would retain the desired properties shown by 2-deoxy-D-glucose. The synthetic strategy for ^{18}F FDG involved the initial development of a new route to the unlabeled compound using elemental fluorine (27) and then adapting this method to labeling with ^{18}F (28,29). As demand for this tracer grew, new higher yield syntheses were sought resulting in a new synthesis of ^{18}F FDG from ^{18}F -labeled acetyl hypofluorite (30). Both routes are shown below. The



synthesis from acetyl hypo ^{18}F fluorite gives a two-fold increase in yield relative to ^{18}F F_2 synthesis.

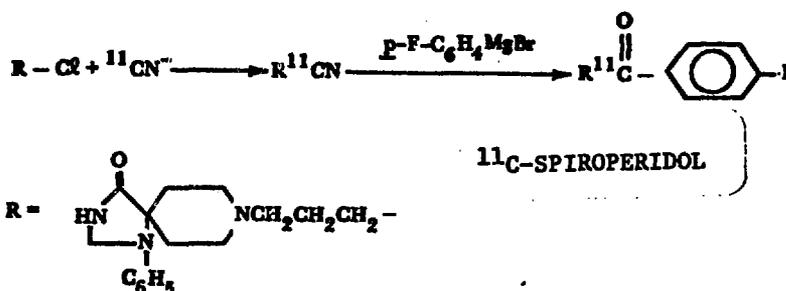
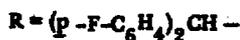
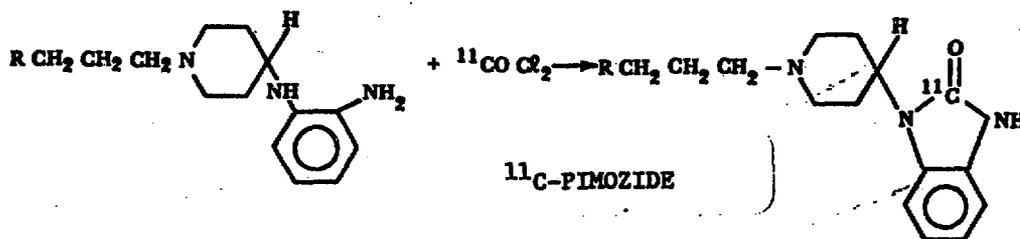
The advantages of studying regional brain glucose metabolism at short time intervals in the same subject has stimulated considerable effort in the

synthesis of appropriate radiotracers. Carbon-11 with its 20.3 minute half-life would allow serial studies to be performed at 2 hour intervals whereas ^{18}F ($t_{1/2}$: 110 minutes) would be required that such experiments be carried out on different days. Therefore, in terms of minimizing temporal variation, carbon-11 is the isotope of choice and a number of ^{11}C -labeled sugars and sugar analogs have been described. For example, ^{11}C -glucose has been prepared by biosynthesis (31-35) as well as synthetic methods (36). ^{11}C -2-Deoxyglucose has been synthesized according to the sequence shown below (37,38) and used in serial studies in human subjects (39). Other ^{18}F and ^{11}C -labeled sugars include 2-deoxy-2- ^{18}F fluoro-D-mannose (28), 3-deoxy-



3- ^{18}F -fluoro-D-glucose (40), 6- ^{18}F fluorogalactose (41), and β -D-glucosyl- ^{18}F fluoride (42), ^{11}C -galactose (43), 3- ^{11}C -methyl-D-glucose (44) and [1- ^{11}C]-mannose (36).

Labeled Amino Acids: A method for the determination of local rates of protein synthesis in brain has been reported recently (45,46). This method requires [^{14}C -carboxy]-L-amino acids of high specific activity. Extension of these studies to humans using PETT has renewed interest in the synthesis of ^{11}C -labeled L-amino acids. Rapid methods for their synthesis include the Strecker synthesis (47) and the carboxylation of α -lithionitriles. The synthesis of D,L-DOPA (48) using the latter method is shown below. Rapid



activity. More recently the triazene decomposition reaction has been used to produce a very high specific activity compound (58-60). The major problem with the triazene decomposition reaction on complex molecules is the low radiochemical yields and the production of complex reaction mixtures which require extensive purification.

Other neurotransmitter receptors which are currently being studied using β^+ emitter labeled ligands are the benzodiazepine receptor (61,62) and the acetyl choline muscarinic receptor (63).

CONCLUSION

A number of problems relating to isotope production and radiotracer synthesis can be cited as important to the continued rapid growth rate in the application of PETT to problems in the biomedical sciences. For example, high level isotope production and labeled precursor synthesis with the new generation of medical cyclotron continues to be a challenge. The production of useful chemical forms from stable isotope targets continues to be an important aspect of these efforts as is the total automation of all aspects of nuclide production and radiotracer synthesis. Perhaps the most challenging problem from the standpoint of radiotracer synthesis is the development of a high yield

synthesis of high specific activity ^{18}F -labeled radiotracers such as the butyrophenone neuroleptics.

Currently, radiotracer development with positron emitters has its major focus on problems in the neurosciences. In each of the major areas discussed above considerable progress and promise are apparent although each area is in a different phase of development. The study of regional brain glucose metabolism represented the first extension of one of the methods of neurochemical autoradiography to humans and although the study of brain protein synthesis and neurotransmitter receptors was begun later, the rewards from the perfection of these methods can also be expected to be great. It is noteworthy that what was once the province of physicians and scientists in the field of nuclear medicine has now attracted basic scientists in the field of neurology, psychiatry, pharmacology, cardiology and oncology. This influx is having considerable impact on the kinds of problems being addressed by these techniques.

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