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Radiotracers for PETT - New Developments and Perspectives

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Recent developments in the application of PETT to problems in the neurosciences and in cardiology and oncology have challenged both research scientists and clinicians to exploit the full potential of this new scientific tool (1-8). In response to the desire of many groups to apply all of the associated PETT technologies to problems in the study of normal and disease states, the concept of regional cyclotron-PETT centers has gained world-wide acceptance. The cyclotron-PETT center consists of an accelerator (usually a small medical cyclotron), a positron emission transaxial tomograph (PETT) and a laboratory for radiotracer synthesis (Fig. 1). The proximity of the cyclotron and PETT as well as their linkage is particularly critical in view of the increasing use of oxygen-15 ($t_{1/2}$ = 2 min) for measuring cerebral blood flow and oxygen metabolism (4). An integral part of each cyclotron-PETT center is a multidisciplinary team of scientists, physicians and support personnel. Such centers, several dozen

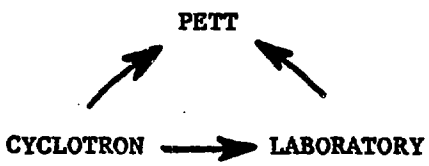

Fig. 1. Diagrammatic representation of the components of an integrated cyclotron-PETT center where the cyclotron supplies radionuclides to the laboratory for radiotracer synthesis and directly to the PETT in the case of short-lived gases such as oxygen-15.

of which are now complete or under development world-wide, serve as resources where existing PETT methods are applied to a growing number of normal and pathological problems and where new problems in the biological and medical sciences are identified and the PETT methods of the future are developed.

Many of the completed cyclotron-PETT centers were developed around an existing cyclotron. Many of these older cyclotrons were used for basic research in physics and nuclear chemistry and as they ceased to be used for this particular application, a number of them were adopted for β^+-emitter production. In 1955, the first so-called medical cyclotron was built and installed in Hammersmith Hospital in London and was used primarily for research and application in medicine. Ten years later, the next wholly dedicated machine was installed in Washington University, Mallinckrodt Institute of Radiology. During the next ten years, a major breakthrough occurred when all of the methodological components i.e. nuclide production, chemistry, instrumentation and biological validation and models for extending the ^{14}C-2-deoxyglucose method (9) to humans using PETT came together. This resulted in the development of the 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}FDG) method (10) which has since been implemented in dozens of institutions world-wide for studying a wide variety of problems in the neurosciences and in cardiology and in oncology. This desire to implement the ^{18}FDG and PETT methods has created a demand for compact cyclotrons which are capable of producing the positron emitters in large quantities while at the same time being relatively small and easy to maintain and operate. Considering present day demands as well as targetry which is well developed

for β^+-emitter production, two particle cyclotrons (proton and deuterons) with proton energies < 20 MeV are most attractive. Cyclotrons having these characteristics (so called "Level II" machines (11)) are manufactured by a number of companies (see Table 1). Most of these machines are capable of accelerating protons and deuterons of fixed energy and high beam currents of 50-100 μA. The general subject of medical cyclotrons has been covered in two recent reviews (11,12).

Table 1. Characteristics of Commercially Available Level II* Cyclotrons

Manufacturer+	Scand MC16F	JSWBC168	BC1710	CG12 Sum 325	CS-18	CP-18**
Protons	17	16	17	16	17	17
Deuterons	8.5	8	10	8	9	9
Other Avail. Particles	yes	no	no	no	yes	no
Proton Current	50	50	50	50	60	50
Deuteron Current	50	50	50	50	100	—

* All machines listed are isochronous AVF. JSW uses a turbomolecular pump for evacuation. All others use oil diffusion pumps.

\+ MC16F Scanditronix; JSWBC168 and BC1710 Japan Steel Works, CGR-SUM, CGR-Sumitomo; CS, CP The Cyclotron Corporation.

** Variable energy negative ion machine.

Radionuclide Production: Choosing the nuclear reactions and developing targetry for producing the required β^+-emitter labeled nuclides requires a careful consideration of target chemistry and this has been the subject of a recent review (13). The use of a proton, deuteron cyclotron to serve the production needs for cyclotron-PETT centers requires the choice of one of the nuclear reactions shown in Table 2. Saturation activities are also given for each of these reactions assuming an available proton or

deuteron energy of 16 MeV or 8 MeV and 10 MeV respectively (Table 3).

Table 2. Production Reactions for β^+ Emitters Using Protons and Deuterons and Level II Cyclotrons

Radionuclide	Nuclear Reaction
Carbon-11	$^{14}N(p,\alpha)^{11}C$, $^{11}B(p,n)^{11}C$, $^{10}B(d,n)^{11}C$
Fluorine-18	$^{20}Ne(d,\alpha)^{18}F$, $^{18}O(p,n)^{18}F$
Oxygen-15	$^{14}N(d,n)^{15}O$, $^{15}N(p,n)^{15}O$
Nitrogen-13	$^{16}O(p,\alpha)^{13}N$, $^{13}C(p,n)^{13}N$, $^{12}C(d,n)^{13}N$

Table 3. Saturation Activities for Principle Reactions; Thick Target Yield

	16MeVp	8MeVd	10MeVd
$^{14}N(p,\alpha)^{11}C$*	173mCi/μA	—	—
$^{18}O(p,n)^{18}F$+	240mCi/μA	—	—
$^{20}Ne(d,\alpha)^{18}F$**	—	69mCi/μA	52mCi/μA

* Bida, G. T., Ruth, T. J., Wolf, A. P., Rad. Acta 27, 181-185 (1980).

\+ Ruth, T. J., Wolf, A. P., Rad. Acta 26, 21-24 (1979).

** Casella, V., Ido, T., Wolf, A. P., Fowler, J. S., MacGregor, R. R., Ruth, T. J., J. Nucl. Med. 21, 750-757 (1980).

It can be expected that in the near future, targetry development for small cyclotrons will experience major breakthroughs and that accelerator manufacturers will maintain the flexibility to respond to these new developments with simplicity of operation and innovation both forming a basis for new designs and new developments.

Labeled Precursors for Radiotracer Synthesis

Table 4 gives a listing of some of the simple ^{11}C, ^{18}F and ^{13}N labeled compounds which are available for organic synthesis. A comprehensive listing of precursors can be found elsewhere (14). 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, ^{11}CO, $^{11}CO_2$ and $H^{11}CN$ are available directly whereas $H^{11}CHO$, $^{11}CH_3I$ and $^{11}COCl_2$ require a more complex experimental setup.

Table 4. Positron-Emitter Labeled Precursors for Synthesis

Isotope	Precursor
Carbon-11	^{11}CO, $^{11}CO_2$, $H^{11}CN$, $H^{11}CHO$ $^{11}CH_3I$, $^{11}COCl_2$
Fluorine-18	$[^{18}F]F_2$, $H^{18}F$ (anhydrous) $H^{18}F$ (aqueous), $CH_3CO_2{}^{18}F$, $ClO_3{}^{18}F$
Nitrogen-13	$^{13}NH_3$, $^{13}NO_2^-$, $^{13}NO_3^-$

The major factor which must be considered in choosing a ^{18}F-target is the chemical form of the ^{18}F required. Both electrophilic and nucleophilic forms of fluorine-18 are required to meet present radiotracer synthesis needs. The targetry for $[^{18}F]F_2$ production and methods for converting it to other electrophilic fluorination reagents is described in the literature (14). Recently, the availability of fluorine-18 (as fluoride ion) in large

quantities from small cyclotrons has been demonstrated using the $^{18}O(p,n)^{18}F$ reaction on a small volume enriched water ($H_2{}^{18}O$) target (15). Since a number of recent breakthroughs in the synthesis of radiotracers using ^{18}F-fluoride do not require conversion to anhydrous $H^{18}F$, the use of these economical $H_2{}^{18}O$ targets is an important development (see Radiotracer Synthesis). Furthermore, with the limitation of low energy and high beam current available with most cyclotrons, the use of a liquid target rather than a gas target reduces density reduction in the beam strike, a phenomenon which leads to a lack of proportionality between beam current and isotope yield in gas targets (16-18).

The measurement and monitoring of the specific activity of labeled precursors or of the tracers produced from them is an essential aspect of many biomedical applications and this has been discussed in a recent monograph (14).

Radiotracer Synthesis

Since the advent of PETT, efforts in radiotracer synthesis have focussed on the synthesis of the radiotracers which could be used to measure blood flow, oxygen metabolism, glucose metabolism, protein synthesis and neurotransmitter receptor properties. More recently, tracers for the measurement of tissue proliferation, tissue pH, drug distribution profiles steroid receptor properties, and lung metabolism have been described. 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 (14). Some recent developments in the synthesis of radiotracers for PETT studies are described below.

Labeled Sugars: The measurement of regional cerebral glucose metabolism has been approached using ^{11}C-glucose itself as well as glucose analogs such as ^{11}C-2-deoxy-D-glucose (^{11}C-2DG) and 2-deoxy-2-[^{18}F]fluoro-D-glucose. The advantages and limitations of each of these approaches have been discussed (4). By far the most widely used method is the ^{18}FDG method and the rapid increase in the number of institutions which are applying the ^{18}FDG method to problems in the neurosciences, cardiology and oncology has provided impetus for developing a number of new synthetic strategies for this compound. The original synthesis of the ^{18}F-labeled compound used elemental fluorine ([^{18}F]F_2) and gave ^{18}FDG in a 10% radiochemical yield (19). A two-fold improvement in yield was recently realized through the use of acetyl hypo[^{18}F]fluorite (20). A number of newer syntheses (some of which have not been used with ^{18}F but which were developed with a view toward ^{18}F-labeling) have also been reported (21-27). The most promising of these methods are those which use fluoride because its use avoids the inherent loss of 50% of the activity which occurs in reagents such as [^{18}F]F_2 (and $CH_3CO_2{}^{18}F$ which is synthesized from it) and KHF_2.

Another example of the analog approach for measuring regional glucose metabolism is the ^{11}C-2DG method (28,29). Except for using a tracer with shorter half life, this method is identical to the ^{18}FDG method. The shorter half life of 20 minutes for carbon-11 compared to the 110 min half life of fluorine-18 allows serial studies to be performed at short time intervals. The ^{11}C-2DG method has been applied to the study of normal variation within a single subject, and to the study of somatosensory

stimulation, cognitive processing and drug intervention. Its synthesis from $H^{11}CN$ is rapid (40 min) yields are moderate (20-30%) and up to 4 preparations can be made in a day (28).

The use of glucose itself has been of considerable interest since the first photosynthetic approach using Swiss chard leaves was reported over a decade ago (30,31). More recently ^{11}C-labeled glucose has been prepared using green algae along with details of remote manipulations and purification (32). A chemical synthesis of ^{11}C-glucose and mannose labeled at C_1 has also recently been described (33). The multiciplicity of ^{11}C-products which would be present shortly after injection of the ^{11}C-glucose require rapid PETT scans and blood volume correction.

The measurement of glucose transport has been approached using 3-[^{11}C]-methyl-D-glucose (34,35). While ^{11}C-glucose and 3-[^{11}C]-methyl-D-glucose have not been widely applied to brain studies, the more widespread use of PETT and the existence of models for converting PETT images to biochemical information may result in the increased exploration of the medical application of these as well as a variety of other different tracers.

Labeled Amino Acids for Use in the Protein Synthesis Model: Labeled amino acids are of interest both for studying protein metabolism and neurotransmitter receptor populations. The 1-^{11}C-L-amino acids used in the Sokoloff model (36,37) are synthesized by the Strecker synthesis although other methods such as the carboxylation of an isonitrile can also be used (38,39). Resolution methods include the use of chiral HPLC columns (40) D-amino acid oxidase (41) or, in the case of tryptophan, by binding

selectively to human serum albumen (42). The synthesis of ^{11}C-L-methionine for measuring protein synthesis is well described in the literature ((43) and references contained in (14).

Labeled Neurotransmitter Receptor Ligands (butyrophenone neuroleptics, amino acids, benzodiazepine derivatives and peptides): The brain dopamine receptor is of current interest because of its implication in a number of disease states, especially schizophrenia (44). Dopamine receptor ligands labeled with β^+-emitters include ^{11}C-pimozide (45), ^{11}C-spiroperidol (46), radiobrominated-bromospiroperidol (47), and ^{18}F-labeled haloperidol (48-51) and spiroperidol (52-56). Butyrophenone neuroleptics pimozide and spiroperidol are labeled with ^{11}C using ^{11}C-phosgene and ^{11}C-cyanide respectively. ^{18}F-Labeled haloperidol was first synthesized by the Schiemann reaction (49) to give a radiotracer of relatively low specific activity. The triazene decomposition reaction explored as a route to very high specific activity ^{18}F-haloperidol and spiroperidol (50,51,53-56). However, 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 (56). A recent breakthrough in ^{18}F-labeling of neuroleptic drugs was made when it was discovered that ^{18}F could be substituted for ^{19}F, NO_2 and Cl groups on activated aromatic rings (57-59). This observation has been extended to the synthesis of NCA ^{18}F-spiroperidol in sufficiently high yield and purity to begin PETT studies in baboons (52).

The study of dopamine distribution in the brain has also been approached using labeled DOPA or a suitable derivative which crosses the

blood-brain-barrier and is converted *in situ* to dopamine via DOPA-decarboxylase (39,60). Both carbon-11 and fluorine-18 syntheses have been devised to meet this requirement. ^{18}F-Labeled 5-fluoro DOPA (61,62) and, more recently, 6-fluoro DOPA were first reported for this purpose (63,64). More recently, synthetic strategies were developed for labeling amino acids in metabolically inert positions (2 and 3) via the ^{11}C-labeled substituted benzyl chloride or benzaldehyde (65,66).

β^+-Emitter labeled radiotracers have been used to study the benzodiazepine receptor in baboons. For example, ^{11}C-labeled flunitrazepam has been synthesized (67) and shown to be displaced *in vivo* with lorazepam (68). More recently a synthetic route to ^{75}Br-labeled 1,4-benzodiazepine derivatives were reported (69). Labeling efforts focussed on those compounds which exhibited a useful degree of pharmacological activity at low dose and therefore were predicted to have a high degree of specific receptor binding and this was verified by comparing their receptor affinities to the potent drug flunitrazepam.

The synthesis of some ^{11}C-methionine containing opiate peptides (66) using ^{11}C-methyl iodide as a labeled precursor has also been described as has the synthesis of the potent opiate agonist ^{11}C-etorphine (70).

The development of tracers which allow the acetyl choline muscarinic receptor to be probed *in vivo* has resulted in the synthesis of ^{11}C-labeled quinuclidinyl benzilate methiodide (71). This tracer has been shown to localize in the myocardium and the mechanism of localization was shown to be due to receptor binding (72).

Other Labeled Tracers for PETT: The search for the ideal tracer for measuring cerebral blood flow has lead to the synthesis and investigation of

a number of tracers including ^{11}C-alcohols (73,74), ^{11}C-labeled iodoantipyrine (75) and ^{18}F-labeled antipyrine (76-78,78a) and alkyl fluorides (79-81). Recent evaluation in baboons demonstrated ^{11}C-butanol as the ideal standard with which to compare other potential flow tracers (82).

Another area of application for PETT is the development of radiotracers for myelin imaging. Such a tracer should be lipophilic and unmetabolized during the imaging time and freely permeable to be blood-brain-barrier. The value of such a tracer would be to detect demyelination in diseases such as multiple sclerosis. ^{11}C-Labeled ethers were prepared for this purpose (83). They were found to be rapidly metabolized in vivo precluding their use (84). Two other potential myelin probes ^{11}C-diphenylmethanol (85) and propyl[^{18}F] fluoride (86), have been synthesized and are in the initial stages of investigation.

Recently the measurement of tissue pH using PETT has been addressed and ^{11}C-5,5-dimethyloxazolidine-2,4-dione (^{11}C-DMO) has been prepared and is currently being applied to the study of cerebral ischemia and malignancy (87-89).

The development of tracers for the measurement of tissue proliferation has been of interest especially in view of their potential use to monitor response to chemotherapy. A number of ^{11}C and ^{18}F-labeled purines, pyrimidines, nucleotides and nucleosides have been prepared and are in the initial stages of evaluation (90-94).

The search for a gamma-emitting estrogenic receptor ligand which has a high affinity has been approached by labeling and evaluating both natural and synthetic compounds (95). Such a tracer would be useful in scintigraphic detection of tumors and their metastases as well as in predicting the response of breast cancer to hormonal therapy. Tritium labeled molecules have been studied in order to select priorities for labeling with gamma or positron emitters (96). The requirement for high specific activity is important here and approaches for labeling with high specific activity are exemplified by the development of synthetic strategies which focus on the use of fluoride ion as a precursor (97,98).

The use of β^+-emitter labeled tracers for studying non-ventilatory lung function was suggested several years ago and a number of ^{11}C-labeled tracers were prepared and evaluated (99-101). Interest in using PETT to further explore the lung's ability to extract endogenous and exogenous amines in health and disease has continued with other lipophilic amines being evaluated (102).

The application of β^+-emitter labeled drugs and PETT to the study of regional pharmacokinetic offers the possibility of correlating a drug's therapeutic efficacy with its regional concentration. For example, the regional kinetics of diphenylhydantoin, a widely used anticonvulsant drug have been studied using ^{11}C-diphenylhydantoin (103).

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 and a number of breakthroughs in isotope production and new synthetic strategies have emerged in the past year.

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 fields of neurology, psychiatry, pharmacology, cardiology and oncology. This influx is having considerable impact on the scope of problems being addressed by these techniques. In a more general sense, one PETT instrumentation will provide resolution in the 5 mm range is already emerging. The present PETT methods will become more standardized. Models

will continue to be refined and difficult questions relating to normal variation and the statistical significance of observed alterations in metabolism will be addressed. The integration of PETT into other imaging modalities such as nmr will be undertaken. Although the question of whether PETT will remain a scientific tool or whether it will become an essential clinical tool required to make rational decisions on the design of therapy for certain diseases, still remains unanswered, one can see now that efforts directly toward its practical use are highly promising.

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