

RADIOTRACERS IN PETT: STRATEGIES FOR IN VIVO RECEPTOR ACTIVITY, SCHIZOPHRENIA, AND ALZHEIMER'S DEMENTIA STUDIES. Alfred P. Wolf, Chemistry Department, Brookhaven National Laboratory, Upton, NY 11973

The application of radiotracers labeled with positron emitters to probe brain biochemistry coupled with Positron Emission Tomography as the assay device has opened new vistas for studying brain and heart biochemistry in normal and disease states (7). The choice of tracer is paramount since it must be amenable to biomodeling and useful as a probe for a particular function or biochemical pathway in vivo. Questions to be addressed include: (A) Criteria for choice of tracer and label to be used; ^{11}C , ^{13}N , ^{15}O or ^{18}F . (B) Nuclide production method and synthetic strategy for a particular radiotracer. Emphasis will be on carbon-11 and fluorine-18 (4). (C) Dynamic studies of neuroleptic drugs in baboons. (D) The Test-Retest paradigm for task and drug intervention studies. (E) Application to Alzheimer's Disease, Chronic Schizophrenia and other disorders.

The preparation of the radionuclide to be used is usually carried out in-house because of the short half-lives involved; ^{11}C = 20.4 m, ^{13}N = 9.96 m, ^{15}O = 2.07 m, ^{18}F = 109.7m. The half-life of fluorine-18 is sufficiently long to allow transport and use within a 800-1200 km radius. Methods of production are readily available: $^{14}\text{N}(p,\alpha)^{11}\text{C}$, $^{16}\text{O}(p,\alpha)^{13}\text{N}$, $^{13}\text{C}(p,n)^{13}\text{N}$, $^{14}\text{N}(d,n)^{15}\text{O}$, $^{15}\text{N}(p,n)^{15}\text{O}$, $^{18}\text{O}(p,n)^{18}\text{F}$, $^{20}\text{Ne}(d,\alpha)^{18}\text{F}$. These radiotracers can be converted on stream, or with 5 to 10 min delays post irradiation, to the labeled precursors necessary for synthesis (7). All too often a synthesis is conceived and effected with little consideration of the use to which it is to be put. This is particularly evident in the neuroleptic and radioligand-for-receptor study areas. The specific activity achievable, the time course of the study, and the metabolic fate of the e.g., neuroleptic, must be considered before a synthetic procedure is chosen. Fluorine-18 is perhaps one of the most useful radionuclides but its position in the compound must be carefully chosen so as not to add to the complexity of probing a specific biochemical pathway.

The specific activity problem becomes painfully evident when considering the neuroleptics and much effort has been directed to syntheses leading to NCA (no-carrier-added) or CF (carrier free) compounds (4,6). While the use of ^{11}C -labeled spiperone has certain advantages in human experimentation relative to dose and multiple intervention and has been effectively used in baboons (1) the use of ^{18}F -labeled spiperone prepared via a new facile NCA synthesis has shed new light on receptor activity in the live baboon brain when studied over an eight hour period (2). Using ^{18}F -spiperone SA $\approx 2 \times 10^4$ Ci/mmol (factor of ~ 100 dilution from CF), a one compartment system with a driving function as model, blocking agents such as butaclamol and ketanserin, assay of the live adult female baboon striatum over the 8 hr period, and assay of the parent compound in plasma, it is apparent that residence times in the living tissue and those estimated from in vitro tritium data are at variance. Occupancy rises to a maximum for ^{18}F benperidol and ^{18}F haloperidol after ~ 25 minutes and for ^{18}F spiperone after ~ 75 minutes, but the striatum concentration of ^{18}F -spiperone and benperidol remain nearly constant over an eight hour period whereas ^{18}F haloperidol concentration starts falling almost immediately to half its

MASTER

EAB

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

maximum value at 8 hrs. Plasma concentrations show similar temporal patterns for all three compounds. The best fit to our current data gives a preliminary "off" rate constant of 0.0057 min^{-1} . The synthetic aspects of preparing ^{18}F -labeled butyrophenones involve the use of nucleophilic aromatic displacement reactions (3a,b). High SA will be addressed as will other aspects of using a variety of labeling techniques in other psychoactive compounds.

The measurement of brain glucose metabolism and oxygen consumption requires ^{18}F -fluorodeoxyglucose, ^{11}C -deoxyglucose and ^{15}O - O_2 . High yield syntheses of the two deoxy sugars are now available and will be discussed (5a,b). Results in the Test-Retest paradigm using ^{11}C -deoxyglucose as the metabolic probe, allowing task or drug interventions between studies on the same day using the individual as his own control, have raised questions as to applicable baselines for assessing brain metabolic activity when the intervention is used. For example, typical group mean changes for regions involved in cognitive activities were 6% (SD 3%) and for cerebellum and thalamus were 2% (SD 1%) when the individuals studied twice on the same day were at "rest" for both studies. Studies in Alzheimer Dementia and Chronic Schizophrenia will be discussed using the metabolic probes previously mentioned.

Another approach to the use of positron emitter labeled tracers and PET involves the use of these tools to study pharmacodynamics in living non-human primates since the tracers can be used not only to study time course and site specificity in all organs of the body, but with appropriate models as e.g., those for metabolic processes, receptor activity, and protein synthesis they can be used to aid in determining the detailed biochemical basis for physiological response in a wide variety of studies. Positron emitter labeled compounds for probing brain biochemistry have proven to be powerful tools for studying neuropharmacology in vivo and for delineating specific pathophysiology in a variety of psychiatric disorders.

The work presented here represents collaborative efforts between BNL and NYU Medical School, University of Pennsylvania Medical School, University of Rome, the CNR Laboratory at Montelibretti, and Los Alamos National Laboratory. Our work is supported by OHER, DOE and also NIH Grant Nos. 15638 and 15380.

1. Arnett, C.D., Fowler, J.S., Wolf, A.P., Logan, L., MacGregor, R.R., (1984): Biol. Psych. (in press).
2. Arnett, C.D., Shiue, C.-Y., Fowler, J.S., Wolf, A.P., Logan, J.: BNL work in progress.
3. (a) Attina, M., Cacace, F., Wolf, A.P. (1983): J. Chem. Soc. Chem. Comm. 108 (1983). (b) Shiue, C.-Y., Watanabe, M., Wolf, A.P., Fowler, J.S., Salvadori, P. (1984): J. Label. Compds. Radiopharm. (in press).
4. Fowler, J.S. and Wolf, A.P. (1982): In: "The Synthesis of Carbon-11, Fluorine-18 and Nitrogen-13 Labeled Radiotracers for Biomedical Application" Nucl. Sci. Series, Nat'l. Acad. Sci. NAS-NS-3201, NTIS, Springfield, VA.
6. Cf. Welch, M.J., Kilbourn, M.R., Mathias, C.J., Mintun, M.A., Raichle, M.E. (1983): Life Sci. 3(3):1687-1693.
5. (a) Shiue, C.-Y., Salvadori, P.A., Wolf, A.P., Fowler, J.S., MacGregor, R.R. (1982): J. Nucl. Med. 23 899-903. (b) Tewson, T.J. (1983): J. Nucl. Med. 24:718-721.
7. Wolf, A.P. (1981): Sem. Nucl. Med. 11(2):2-12.