DOI 10.1007/s00702-004-0272-2
J Neural Transm (2005) 112: 319–330

Journal of Neural Transmission

Micropet imaging: in vivo biochemistry in small animals*

V. Sossi[1,2] and **T. J. Ruth**[1]

[1] University of British Columbia/TRIUMF PET Program, and
[2] Physics and Astronomy Department, University of British Columbia, Vancouver, B.C., Canada

Received May 12, 2004; accepted December 11, 2004

Summary. Significant technological advancements required for imaging physiological function in small animals have been achieved in the last few years. Dedicated small animals PET scanners are now achieving resolutions that approach the one obtainable by autoradiographic methods, while still maintaining enough detection sensitivity to reliably measure biologically relevant parameters such as binding potentials or rate constants. Such developments have enabled researchers to explore in-vivo rodent models of human disease. The future in imaging now lies in the development of multi-modality imaging approaches, while the big challenge in the next few years will be for the chemists to develop tracers that are more specific and reflective of the functional condition under investigation, while miniaturizing the chemical synthesis related instrumentation.

Keywords: Small animal imaging, radiotracers, positron emission tomography.

Introduction

For years researchers have used small animal models of human disease to address questions by using radiotracers and autoradiography. While providing high spatial resolution, these techniques suffer from two major shortcomings: data can only be collected post-mortem and might not provide a true representation of in-vivo processes. Likewise they do not allow for the performance of longitudinal studies on the same subjects. The temporal progression of a process under investigation is generally obtained by using a large group of animals, supposedly treated in an identical fashion, and by sacrificing a subset at particular time points of interest. Such procedures are not only costly in terms of animal life, but also introduce inter subject variability into the results. Positron emission tomography (PET) is a functional imaging modality that overcomes both these shortcomings: functional information can be obtained in-vivo, on live animals. Repeated and thus longitudinal studies in the same animals (Nikolaus et al., 2003; Umegaki et al., 2003) now become possible. PET is based on the

* Lecture, 11th IWCN Congress, September 14–16, 2003 (Campbell River, BC, Canada)

administration of radiotracers labeled with positron emitting radioisotopes where the chemical form of the radiotracer is designed to investigate a specific biological site or process of interest, such as measuring glucose uptake rates or specific receptor populations. From a mostly visually based imaging modality, PET has over the course of the last two decades evolved into a fairly accurate quantitative imaging tool where the strength of many processes can now be measured and compared in terms of binding potentials or rate constants. Factors contributing to this evolution include a many fold increase in the instrumentation spatial resolution and detection sensitivity, significant improvements in data quantification and image reconstruction algorithms and development of radiotracers that are both highly selective for the process of interest and can reach the target of interest through a non-invasive route (Myers, 2001; Hume and Myers, 2002; Cherry and Gambhir, 2001).

PET imaging has been in use for several decades for human brain and whole body imaging, first only as a research tool, now gaining acceptance as a diagnostic imaging modality in selected applications such as oncology and, very recently, as an aid in the diagnosis of Alzheimer's disease. Compared to human PET scanning, small animal PET presents new challenges, both of instrumentation and biological nature. However it also offers new exciting opportunities such as the in-vivo testing of new pharmaceuticals while at the same time allowing for the possibility of direct correlation between in-vivo and in-vitro measurements thus indirectly providing a deeper understanding of the human PET measurements. For the most part the use of small animal scanning has been dominated by research in oncology because of the existing animal models of tumor biology and the relative ease of placement of the tumor in a location with low background. With the increased availability of animal models of disease, such as, for example, Parkinsons's disease and dyskinesia, small animal imaging has been steadily expanding into the areas of brain and neuroreceptor imaging with a variety of different tracers. The discussion of the small animal imaging related challenges, some addressed, some as yet unresolved, together with the description of the new opportunities will be the subject of the next paragraphs.

Challenges in small animal PET imaging

a. Instrumentation related challenges

The biggest instrumentation challenge that needed to be overcome to successfully apply PET imaging to small animals was to increase spatial resolution, while still maintaining high detection sensitivity. For example, the spatial resolution of traditional human PET scanners ranges typically from $(4\,\text{mm})^3$ to $(9\,\text{mm})^3$, while the size of a rat or mouse organ is orders of magnitude smaller compared to the size of the corresponding human organ (Fig. 1).

In PET, radiotracer decay is measured by detecting in temporal coincidence the two 511 keV γ rays originating from positron decays. A PET scanner is thus essentially a γ detection device; small detectors with high γ stopping efficiency were thus needed to achieve the desired performance goals. A significant milestone for the imaging community was achieved by the introduction of Lutetium

Fig. 1. Relative size of a human, rat and mouse brain

Orthosilicate (LSO) as the γ detection material. Its high density ($7.13\,g/cm^3$ compared to $7.4\,g/cm^3$ for BGO and $3.67\,g/cm^3$ for Na(I), the other two commonly used scintillation materials in γ detection in medical imaging) and high light yield (75% of that of Na(I), typically used as reference in determining light output – compared to 15% for BGO)) have allowed for the reduction in the size of individual crystals to dimensions of the order of a couple of millimeters or less (Fig. 2) thus leading to spatial resolutions in the range of $(1\,mm)^3$–$(1.8\,mm)^3$ while still maintaining absolute γ detection sensitivities of approximately 2% (Tai et al., 2003; Chatziannou, 2002; Knoess et al., 2003). Although now the most commonly used detector material in small animal scanners, LSO is by no means the only candidate: commercial and research groups have been successful in designing other versions of animal scanners

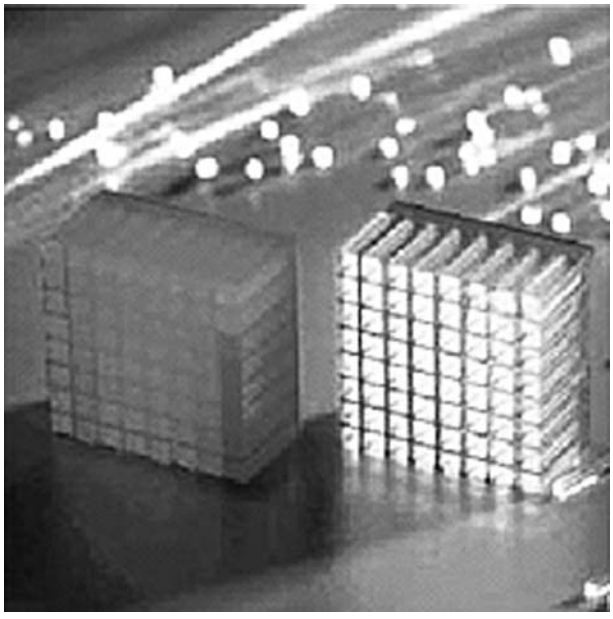

Fig. 2. LSO crystals used and light-guides used in the Concorde microPET. Crystal size $2.1\times2.1\times10\,mm^3$

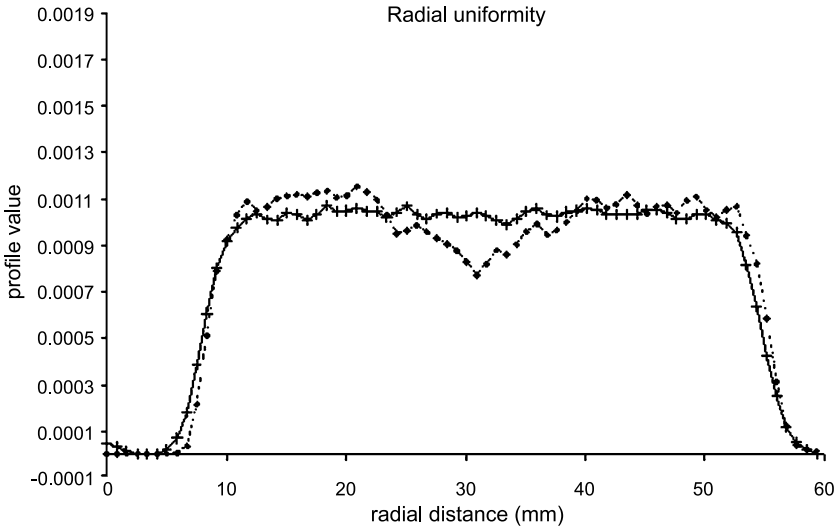

Fig. 3. Radial profile of a cylindrical phantom with a non-optimized normalization (diamonds) and an optimized normalization (+) method. Ideally the profile should be completely uniform (straight). A clear improvement is observed with the optimized detector normalization algorithm

(Jeavons et al., 1999; del Guerra et al., 2002) and are still very actively researching new γ detection materials and scanner designs (Weber et al., 1999; McElroy et al., 2003; Seidel et al., 2003). The remaining challenge is to increase the detection sensitivity by an order of magnitude without decreasing spatial resolution.

It is important to notice that hardware advances are being paralleled with equally impressive steps in the development of software algorithms that provide more accurate data quantification and image reconstruction. Figure 3, for example, shows the improvement in image uniformity that can be achieved with a more accurate detector calibration method (Camborde et al., 2004). Most of this work is common to both small animal and human scanners and facilitated by the continuously increasing computing power.

b. Biology related challenges

There are at least two features that are very clearly distinct in animal compared to human scanning: the need to administer anesthetics and the small physical size of the animals.

Both these distinctions have a direct impact on PET imaging. Several studies have shown that anesthesia affects ligand-receptor binding (Votaw et al., 2003). Data from our centre also confirm that the effect of anesthesia affects PET measures in an anesthetic, tracer and receptor type dependent manner as shown in Fig. 4. This consideration is of extreme importance when multi-tracer studies need to be performed on the animals to assess relative changes in different receptor activity. This is the case, for example, when animal models of disease are used to investigate disease or treatment induced compensatory changes observed in Parkinson's Disease human studies (Lee et al., 2000). An instrumentation-related potential answer to this problem is the development of

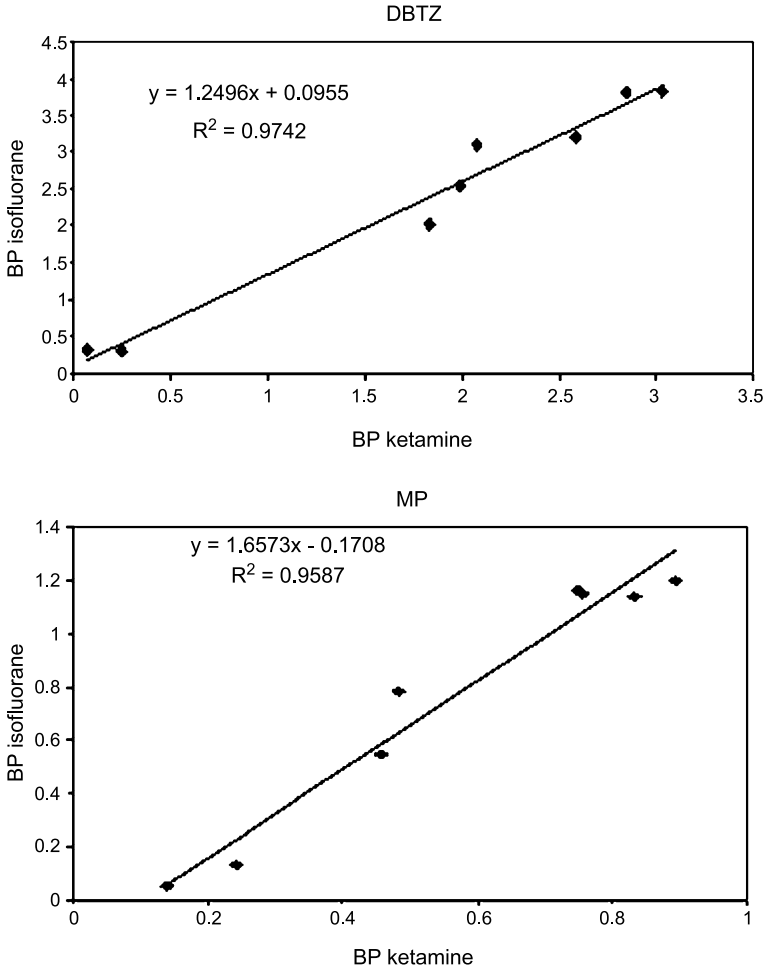

Fig. 4. Binding potential obtained with isofluorane (y-axis) and ketamine/xylazine (x-axis) for ^{11}C-methylphenidate (MP), a dopamine membrane transporter marker (right), and ^{11}C-dihydrotetrabenazine (DTBZ), a marker for the vesicular transporter VMAT2 (left). Each point represents a striatum of each rat (total 4 rats). The relationship between the binding potentials measured under the two anesthetic conditions varies as a function of tracer

small PET cameras that can be fixed to the animal head so as to allow the scanning of the animal in the awakened state (Woody et al., 2004).

The small size of the animals limits the amount of the tracer that can be administered in a scanning session: PET is based on the tracer principle, that is, the administered radiotracer must not influence the process under investigation. In receptor imaging this is satisfied when the tracer does not occupy more than 1% of the available receptors (Hume et al., 1998). This requires tracers to be produced at very high specific activities (generally >1 Ci/μmole) and limits the amount of radioactivity that can be injected, thus rendering detection sensitivity even more important.

The second complication due to the small physical size is the fact that the size of the animal's blood pool is very small. This has direct implications on the applicability of biological models that are applied to the PET data to extract

biologically relevant parameters such as binding potentials and process rate constants. Many of this models in-fact relay on an input function derived from the radiotracer concentration in plasma, measured by extraction of several blood samples. Such blood sampling is often not possible with these small animals, therefore analysis methods that utilize tissue input functions must be used. Such methods require a region where there is no specific binding of the tracer and appropriate regions must be accurately identified for each tracer. Conversely, some research groups are looking into the possibility of measuring the plasma input function from the image of an animal organ, such as the heart (van der Weerdt, 2001). However this is in practice only feasible when the radiotracer does not undergo significant metabolism: the PET scanner in-fact only detects radioactivity and is not able to separate the chemical form of the radioactively labeled substance.

New opportunities

In order to graphically illustrate the potential of PET imaging, a side to side figure of a PET image and an autoradiographic image of rat striata obtained with the monoamine vesicular transporter VMAT2 marker ^{11}C-dihydrotetrabenazine (DTBZ – Vander Borght et al., 1995a, b; Chan et al., 1999) is shown in Fig. 5. In this case the PET image was obtained microPET® R4 scanner (Knoess et al., 2003). Although the superior resolution obtained with the phosphor imager is still visible, it is also noticeable that the resolution achievable with PET is rapidly approaching that available with postmortem measures.

a. Use of rat models to investigate disease – possibility of interventions

With all methodological concerns properly addressed, small animal PET can be successfully used to quantitatively investigate functional changes occurring as a consequence of disease or specific interventions. For example, a commonly used rat model of Parkinson's disease is striatal lesioning using 6-hydroxydopamine (6HODA). Recent studies in our laboratory have demonstrated the ability to quantify differences in the DTBZ binding potential (Logan et al.,

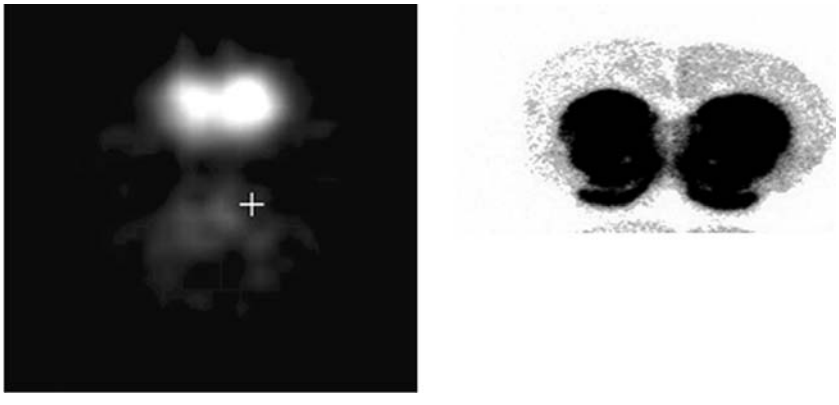

Fig. 5. A phosphor imager (right) and a microPET® image (left) of rat striata

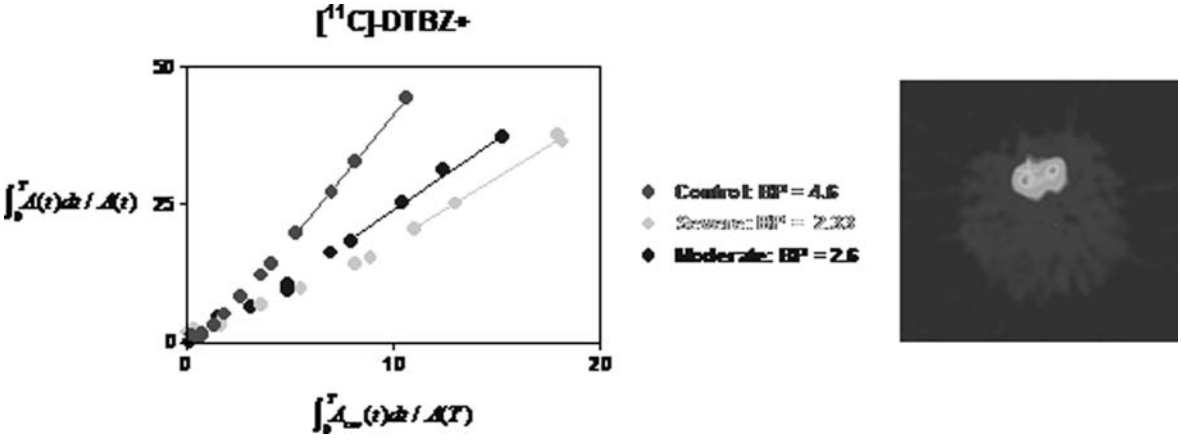

Fig. 6. Example of a Logan plots used to determine the DTBZ binding potential for a healthy, a moderately and severely rat striatum, together with a microPET image obtained from a DTBZ scan of a healthy rat brain

1996) between a healthy, a moderately and a severely lesioned rat (Fig. 6). Since longitudinal studies on the same animals are possible with PET, it now becomes feasible to perform more complex studies, such as, for instance, investigate chronic vs. acute effects of treatment, or simply effects of disease as approximated by the particular animal model. Another exciting example is the use of ^{18}F-EF5 (Dolbier et al., 2001) PET imaging in Shionogi tumor models in mice to investigate hypoxia levels and related androgen dependence in prostate cancer (Fig. 7) (Miyake et al., 1999).

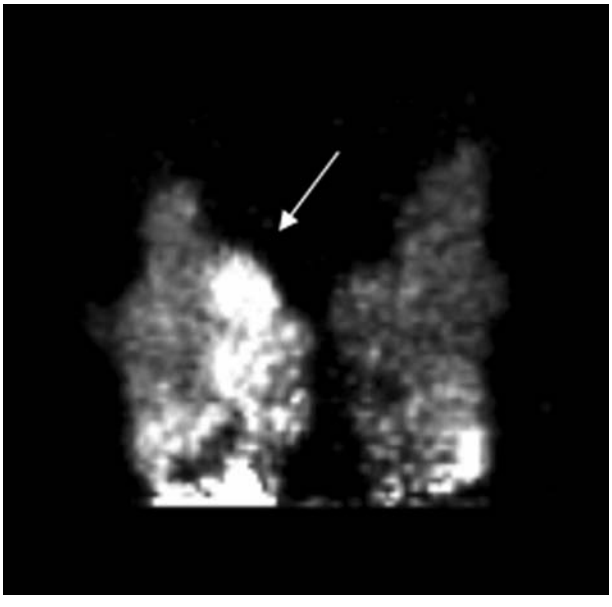

Fig. 7. ^{18}F-EF5 Scan of mice with an androgen independent tumor (left) and an androgen dependent tumor (right). The first type is supposed to be more hypoxic as confirmed by a higher ^{18}F-EF5 uptake (see arrow) compared to the same area on the mouse imaged on the right side. Courtesy of Dr. D. Yapp, BC Cancer Agency

b. Testing of new drugs and their efficacy

Small animal PET imaging is an ideal tool in the process of new drug development and evaluation of treatment efficacy (Campbell, 1995). PET imaging can be used to either follow a drug distribution and metabolism via the use of the labeled drug or to measure efficacy of action through the use other PET tracers as surrogate markers of the drug role in altering function (Langstrom, 1995). While labeling the drug directly may present some challenges, the labeled drug is seen as an important tool for those compounds directed at brain function since an estimate of degree (and even whether) a drug penetrates the blood-brain-barrier is required before further drug assessment. In addition the concentration at which a drug has affective action is often associated with plasma concentrations when in fact this relationship may not really be measuring the effect of the drug in the brain. The true effect can be measured via PET, either with labeled drug or with surrogate molecules.

In drug design a particular neuronal system is to be altered through blocking enzymes, intercepting transmitters or occupying receptors. Using tracers that are sensitive to these changes can provide the needed information in a time frame measured in minutes to hours as opposed to waiting for a pharmacological effect which may take days if not weeks. As mentioned in the introduction, the ability to assess the effects of an intervention longitudinally, on the same animals, significantly reduces the variability of the final results and makes better, more efficient use of the animals themselves.

c. Comparison with post-mortem measures

A unique advantage presented by small animal PET scanning is the ability to investigate correlations between imaging data and more traditional, fairly invasive procedures such as in situ microdialysis: Fig. 8 shows an example of

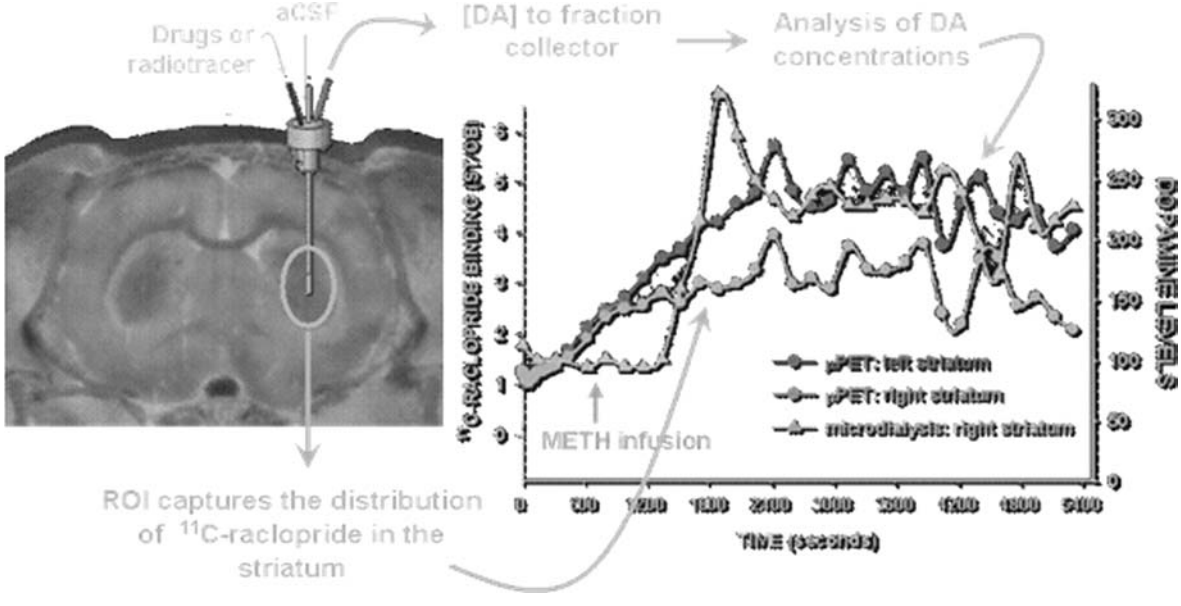

Fig. 8. Strategy for combined microPET/microdialysis studies of DA transmission. Courtesy of W. Shiffer, Brokhaven National Laboratory

the time course of the D2 dopamine receptor antagonist ^{11}C-raclopride in the rat striata overlaid on the time course of extracellular dopamine concentration release as a consequence of methamphetamine infusion. Such comparative approaches will contribute to a better understanding of the information provided by each technique itself and will lay the groundwork for a more comprehensive, possibly multi-modal investigation of disease induced functional changes.

d. Radiotracer and chemistry development

Tracer development is an extremely important component of PET imaging. The PET scanner only measures radioactive decays and cannot by itself identify a biological process of interest. This is accomplished by careful radiotracer design and development to make it as specific as possible for the relevant biological sites and processes, while minimizing its binding to other tissue types (Kawamura et al., 2003; Okarvi, 2001). As the imaging instrumentation becomes more powerful, there is an increasing demand for new tracers as more sites and processes become potentially observable in-vivo. In addition to undergoing in-vitro validation however, the new tracers must undergo a rigorous validation of their behavior in-vivo and, where necessary, new imaging protocols and analysis methods must be developed. Presently there is a number of small molecules that have been used in human PET scanning for years as well as in small animal autoradiographic studies using the ^{3}H and ^{14}C labeled versions. In order to have sufficient signal for the PET scanner the tracers have to be of sufficiently high specific activity (radioactivity units per mass) to provide a high-count rate while not violating the tracer principle. The specific activity required to maintain this principle is on the order of 1 Ci/μmole (Hume et al., 1998). Such specific activities would thus result in the injection of tens of picomoles of tracer. In addition to the need for high specific activity there is a need for high radioactivity concentration (radioactivity units per volume of solution). This requirement stems form the fact that the volume that can be injected is on the order of 0.5 mL, maximum. While there are no requirements to produce the tracers under regulatory conditions, it is obvious that the tracer must be of the highest purity in order to preserve the integrity of the study.

The development and use of PET tracers can be viewed as covering two major areas, 1) tracers that can be used as surrogate markers for biological processes and 2) those tracers that are specific for a particular process, whether it is intended to measure enzyme activity or receptor concentration or the expression protein synthesis. A major hindrance in tracer development is the complex nature of the synthesis process itself. While major steps have been made to simplify the syntheses steps (Wilson et al., 2000; Studenov et al., 2003, 2004) there are still areas in need of improvement such as miniaturization of the synthesis instrumentation. Miniaturization provides the opportunity to use small amounts of starting materials and radioactivity that would make the purification simpler and easier. Simple solid phase columns could be used instead of cumbersome high performance liquid chromatography. In addition if the miniaturization can be realized it is conceivable that multiple compounds could be prepared in parallel for testing with a single supply of radioisotope. This can be viewed as the radiochemist's attempt at screening compounds.

Future directions in small animal imaging

There is presently a strong trend towards the development of PET scanners with even higher sensitivity and resolution and towards an integrated, multi-imaging-modality approach to the investigation of biochemistry in small animals. Combined PET and MRI or CTI scanners are being investigated (Mackewn, 2004; Lecomte, 2004) as well as methods to combine information from optical and functional imaging (Tsyganov, 2004).

In terms of PET, ultimately the true power of this functional imaging relies on the availability of tracers that are specific to the biological question pursued (Rowland et al., 2002). At present most tracers measure receptors or enzymatic function which may be altered in disease or through pharmacological intervention. However, most of these changes are in response to the intervention and do not reflect the underlying process itself, the changes in gene expression. The ability to visualize these processes is the Holy Grail for functional imaging. A step in this direction has been achieved with the development and use of reporter genes whereby easily recognized regions of gene are linked to the regulatory regions of genes of interest. Then a tracer specific for the recognizable region is used to probe the time distribution of the *reporter* (Herschman, 2004).

Thus the major research efforts over the next several years will be towards finding molecular systems that are able to measure these changes. The use of large molecules such as peptides or oligonucleotides may provide the vehicle.

Conclusion

In order to provide insights into the fundamental biochemistry underlying function and disease mechanisms it is important to understand the biochemical processes at several different levels, from in-vitro biochemistry to the in-vivo interaction between the fundamental process and its surroundings. This is a profound endeavor that can only be accomplished with a synergistic approach that fully exploits recent advances in many different fields ranging from nanochemistry and nanobiology, through various techniques of in-vivo molecular imaging to human scale functional imaging. In this scenario small animal PET together with various animal disease models provides an essential step from the laboratory based molecular research to the understanding of the corresponding function in the human body. Equally important is also the application of small animal PET imaging to drug development and testing (Cherry, 2001; Herschman, 2003; Hume, 2002), where it can provide the link between in-vitro drug evaluation and its first application in human trials.

References

Camborde ML, Rahmim A, Newport DF, Siegel S, Buckley KR, Vandervoort E, Ruth TJ, Sossi V (2004) Effect of normalization method on image uniformity and distribution volume ratio estimates on microPET® R4. 2004 IEEE/MIC Meeting Rome, Italy

Campbell B (1995) Drug development and positron emission tomography. In: Comar D (ed) PET for drug development and evaluation. Kluwer, Dordrecht, pp 25–36

Chan GL, Holden JE, Stoessl AJ, Samii A, Doudet DJ, Dobko T et al. (1999) Reproducibility studies with 11C-DTBZ, a monoamine vesicular transporter inhibitor in healthy human subjects. J Nucl Med 40: 283–289

Chatziioannou AF (2002) PET scanners dedicated to molecular imaging of small animal models. Mol Imaging Biol 4: 47–63

Cherry SR (2001) Fundamentals of positron emission tomography and applications in preclinical drug development. J Clin Pharmacol 41: 482–491

Cherry SR, Gambhir SS (2001) Use of positron emission tomography in animal research. ILAR J 42: 219–232

del Guerra A, Belcari N (2002) Advances in animal PET scanners. Q J Nucl Med 46(1): 35–47

Dolbier WR, Li AR, Koch CJ, Kachur AV (2001) [18F]-EF5, a marker for PET detection of hypoxia: synthesis of precursor and a new fluorination procedure. Appl Radiat Isot 54(1): 73–80

Frese T, Rouze NC, Bouman CA, Sauer K, Hutchins GD (2003) Quantitative comparison of FBP, EM, and Bayesian reconstruction algorithms for the IndyPET scanner. IEEE Trans Med Imaging 22: 258–276

Herschman HR (2003) Molecular imaging: looking at problems, seeing solutions. Science 24; 302(5645): 605–608

Herschman HR (2004) PET reporter genes for noninvasive imaging of gene therapy, cell tracking and transgenic analysis. Crit Rev Oncol/Hematol 51: 191–204

Hume SP, Gunn RN, Jones T (1998) Pharmacological constraints associated with positron emission tomographic scanning of small laboratory animals. Eur J Nucl Med 25: 173–176

Hume SP, Myers R (2002) Dedicated small animal scanners: a new tool for drug development? Curr Pharm Des 8: 1497–1511

Jacobs AH, Li H, Winkeler A, Hilker R, Knoess C, Ruger A, Galldiks N, Schaller B, Sobesky J, Kracht L, Monfared P, Klein M, Vollmar S, Bauer B, Wagner R, Graf R, Wienhard K, Herholz K, Heiss WD (2003) PET-based molecular imaging in neuroscience. Eur J Nucl Med Mol Imaging 30: 1051–1065

Jeavons AP, Chandler RA, Dettmar CAR (1999) A 3D HIDAC-PET camera with sub-millimetre resolution for imaging small animals. IEEE Trans Nucl Sci 46; 3: 468–473

Kawamura K, Elsinga PH, Kobayashi T, Ishii S, Wang WF, Matsuno K, Vaalburg W, Ishiwata K (2003) Synthesis and evaluation of 11C- and 18F-labeled 1-[2-(4-alkoxy-3-methoxyphenyl)ethyl]-4-(3-phenylpropyl)piperazines as sigma receptor ligands for positron emission tomography studies. Nucl Med Biol 30: 273–284

Knoess C, Siegel S, Smith A, Newport D, Richerzhagen N, Winkeler A, Jacobs A, Goble RN, Graf R, Wienhard K, Heiss WD (2003) Performance evaluation of the microPET R4 PET scanner for rodents. Eur J Nucl Med Mol Imaging 30(5): 737–747

Langstrom B, Bergstrom M, Hartvig P, Valind S, Watanabe Y (1995) Is PET a tool for drug evaluation. In: Comar D (ed) PET for drug development and evaluation. Kluwer, Dordrecht

Lecomte R, Bérard P, Pepin CM, Bélanger F, Cadorette J, Convert L, Lepage MD, Leroux JD, Michaud JB, Pratte JF, Robert S, Rouleau D, Selivanov VV, Tétrault MA, Fontaine R (2004) Design considerations for a combined, APD-based μPET/μCT Scanner. Proceedings, 2004 IEEE/MIC Meeting, Rome, Italy

Lee CS, Samii A, Sossi V, Ruth TJ, Schulzer M, Holden JE, Wudel J, Pal P, de la Fuente-Fernadez R, Calne DB, Stoessl AJ (2000) In vivo PET evidence for compensatory changes in presynaptic dopaminergic nerve terminals in Parkinson's disease. Ann Neurol 47: 493–503

Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL (1996) Distribution volume ratios without blood sampling from graphical analysis of PET data. J Cereb Blood Flow Metab 16(5): 834–840

Mackewn JE, Strul D, Hallett WA, Halsted P, Page TA, Keevil SF, Williams SC, Cherry SR, Marsden PK (2004) Design and development of an MR compatible PET scanner for imaging small animals. Proceedings, 2004 IEEE/MIC Meeting, Rome, Italy

McElroy DP, Pimpl W, Djelassi M, Pichler BJ, Rafecas M, Schuler T, Ziegler SI (2003) First results from MADPET-II: a novel detector and readout system for high resolution small animal PET. Nuclear Science Symposium Conference Record, October 19–25, 2003. IEEE Volume 3, pp 2043–2047

Miyake H, Tolcher A, Gleave ME (1999) Antisense Bcl-2 oligodeoxynucleotides inhibit progression to androgen-independence after castration in the Shionogi tumor model. Cancer Res 59: 4030–4034

Myers R (2001) The biological application of small animal PET imaging. Nucl Med Biol 28: 585–593

Nikolaus S, Larisch R, Beu M, Forutan F, Vosberg H, Muller-Gartner HW (2003) Bilateral increase in striatal dopamine D2 receptor density in the 6-hydroxydopamine-lesioned rat: a serial in vivo investigation with small animal PET. Eur J Nucl Med Mol Imaging 30: 390–395

Okarvi SM (2001) Recent progress in fluorine-18 labelled peptide radiopharmaceuticals. Eur J Nucl Med 28: 929–938

Rowland DJ, Lewis JS, Welch MJ (2002) Molecular imaging: the application of small animal positron emission tomography. J Cell Biochem [Suppl] 39: 110–115

Schafers M, Ametamey S, Schubiger PA (2003) Sensitivity or resolution – or both? ''State of the Art Imaging Using Small Animal PET Scanners'' report on the 10th Bottstein Colloquium/2nd Workshop on Basic Research in Molecular Imaging, October 11–12, 2002, Villigen, Switzerland. Eur J Nucl Med Mol Imaging 30: 482–483

Seidel J, Vaquero JJ, Green MV (2003) Resolution uniformity and sensitivity of the NIH ATLAS small animal PET scanner: comparison to simulated LSO scanners without depth-of-interaction capability. IEEE Transact Nucl Sci 50(5): 1347–1350

Studenov AR, Jivan S, Buckley KR, Adam MJ (2003) Efficient *In-Loop* synthesis of high specific radioactivity [^{11}C]carfentanil. J Labelled Cpd Radiopharm 46(9): 837–842

Studenov AR, Jivan S, Adam MJ, Buckley KR, Ruth TJ (2004) Studies of the mechanism of the *In-Loop* synthesis of radiopharmaceuticals. Appl Radiat Isot 61: 1195–1201

Tai YC, Chatziioannou AF, Yang Y, Silverman RW, Meadors K, Siegel S, Newport DF, Stickel JR, Cherry SR (2003) MicroPET II: design, development and initial performance of an improved microPET scanner for small-animal imaging. Phys Med Biol 48: 1519–1537

Tsyganov EN, Antich PP, Kulkarni PV, Mason RP, Parkey RW, Seliounine SY, Shay JW, Soesbe TC, Zinchenko AI (2004) Micro-SPECT combined with 3D optical imaging. Proceedings, 2004 IEEE/MIC Meeting, Rome, Italy

Umegaki H, Ishiwata K, Ogawa O, Ingram DK, Roth GS, Oda K, Kurotani S, Kawamura K, Wang WF, Ikari H, Senda M, Iguchi A (2003) Longitudinal follow-up study of adenoviral vector-mediated gene transfer of dopamine D2 receptors in the striatum in young, middle-aged, and aged rats: a positron emission tomography study. Neuroscience 121: 479–486

Vander Borght TM, Sima AA, Kilbourn MR, Desmond TJ, Kuhl DE, Frey KA (1995a) [^{3}H]methoxytetrabenazine: a high specific activity ligand for estimating monoaminergic neuronal integrity. Neuroscience 68: 955–962

Vander Borght T, Kilbourn M, Desmond T, Kuhl D, Frey K (1995b) The vesicular monoamine transporter is not regulated by dopaminergic drug treatments. Eur J Pharmacol 294: 577–583

van der Weerdt AP, Klein LJ, Boellaard R, Visser CA, Visser FC, Lammertsma AA (2001) Image-derived input functions for determination of MRGlu in cardiac (18)F-FDG PET scans. J Nucl Med 42(11): 1622–1629

Votaw J, Byas-Smith M, Hua J, Voll R, Martarello L, Levey AI, Bowman FD, Goodman M (2003) Interaction of isoflurane with the dopamine transporter. Anesthesiology 98(2): 404–411

Weber S, Herzog H, Cremer M, Engels R, Hamacher K, Kehren F, Muehlensiepen H, Ploux L, Reinartz R, Reinhart P, Rongen F, Sonnenberg F, Coenen HH, Halling H (1999) First results from MADPET-II: a novel detector and readout system for high resolution small animal PET. IEEE Transact Nucl Sci 46(4): 1177–1183

Wilson AA, Garcia A, Jin L, Houle S (2000) Radiotracer synthesis from [^{11}C]iodomethane: a remarkably simple captive solvent method. Nucl Med Biol 27(6): 529–532

Woody CL, Fontaine R, Junnarkar S, Kandasamy A, Kriplani A, Krishnamoorthy S, Lecomte R, O'Connor P, Page C, Pratte J-F, Purschke M, Radeka V, Rampil I, Schlyer DJ, Shokouhi S, Southekal S, Stoll SP, Vaska P, Villaneuva A, Yul B (2004) The RatCAP conscious small animal PET tomography. Proceedings, 2004 IEEE/MIC Meeting, Rome, Italy

Authors' address: V. Sossi, PhD, Pacific Parkinson's Research Centre, Vancouver Hospital and Health Sciences Centre, University of British Columbia, Purdy Pavilion, 2221 Wesbrook Mall, Vancouver, B.C., Canada V6T 2B5, e-mail: vesna@physics.ubc.ca