

POSITRON EMISSION TOMOGRAPHY: MOLECULAR IMAGING OF BIOLOGICAL PROCESSES

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Keywords: functional imaging, positron emission tomography, metabolism, brain receptors, cancer, genes

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Summary

Positron emission tomography (PET) is an unsurpassed method for imaging human biochemical and physiological processes *in vivo*. Unlimited numbers of natural substrates, substrate analogs, and drugs can be labeled for use with PET. This labeling does not change their chemical or biological properties. Minute amounts of biologically active compounds are labeled with positron emitting radionuclides and then administered to the subjects.

The temporal and spatial distribution of these tracers within the body is measured with PET. PET combined with tracer kinetic models measures blood flow, membrane transport, metabolism, ligand receptor interactions, and, recently, also gene expression, noninvasively and quantitatively, in humans. PET has also been used extensively to study cellular metabolism in the brain, heart, and malignant tumors.

1. Introduction: Principles of PET

Positron emission tomography (PET) is a quantitative *in vivo* functional imaging method that can generate information on human physiology and pathophysiology at a molecular level currently unobtainable with other methods. PET is an extremely sensitive and specific imaging tool that allows reliable detection of even subpicomolar concentrations of compounds.

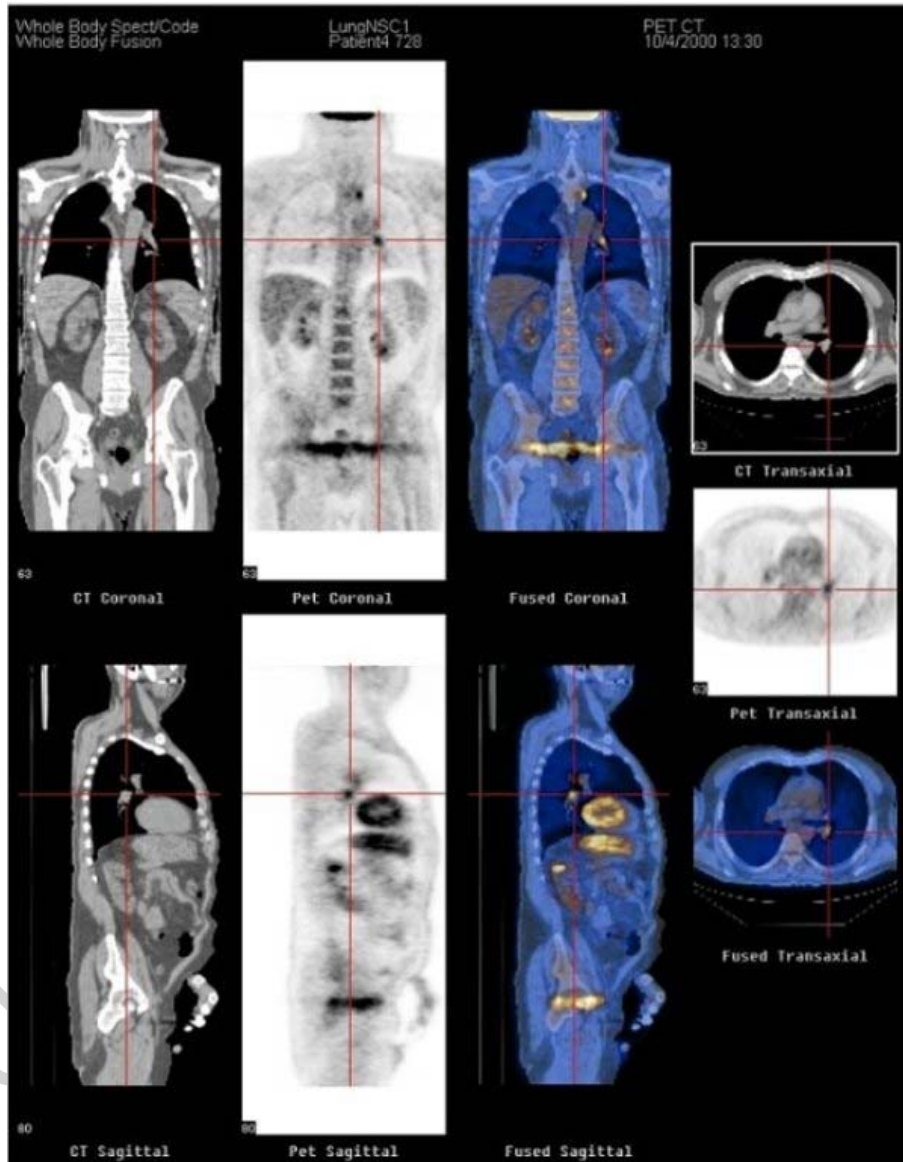


Figure 1. Example of whole body imaging using combined PET and X-ray CT
Source: Image provided by Professor Gustav von Schulthess, Zurich University, Switzerland.

PET is based on the use of short-lived positron emitting radioisotopes, such as carbon-11 ($t_{1/2} = 20$ min), nitrogen-13 ($t_{1/2} = 10$ min), oxygen-15 ($t_{1/2} = 2$ min), and fluorine-18 ($t_{1/2} = 110$ min). Nearly all substrates and drugs can be labeled without changing their physicochemical or pharmacological properties. Due to rapid decay of the positron emitters most PET tracers have to be synthesized on site. The tracer is injected

intravenously into the subject or inhaled as a gas. It is distributed throughout the body via the bloodstream and enters into organs. In tissue, positrons emitted from the nucleus collide with their counterparts—electrons—and the masses of the two particles are converted into two photons emitted simultaneously in opposite directions. PET imaging is based on the detection of these paired photons in coincidence. PET can thus measure the anatomical and temporal distribution of the radiolabeled molecules in the body, since the site of collision is registered by the detector system. Physiological and pharmacological phenomena and biological parameters can be estimated *in vivo* by mathematical modeling of the tissue and blood time-activity curves obtained.

Anatomic information from computerized tomography (CT) and magnetic resonance imaging (MRI) add to the functional information obtained with PET, and the three 3D imaging modalities can be seen as complementary to each other. The image correlation can be facilitated by sophisticated software allowing coregistration of CT or MRI images with PET. Furthermore, PET scanners combined with CT or MRI are now being developed to effectively merge structural anatomy and molecular function into one image. The major emphasis in technical development is on PET and X-ray CT scanners at both patient and small animal levels. Recent years have witnessed the use of the first clinical PET/CT systems, which doubtless will soon be more available (see Figure 1).

Moreover, the recent development of high-resolution micro-PET cameras will open entirely new perspectives for studying genetically engineered small animals. The goal is to provide a similar *in vivo* molecular imaging capability in mouse, rat, monkey, and humans. These devices are being designed to provide high-throughput *in vivo* differential screening of biological responses in transgenic rodents' cell transplants for monitoring of drug effects.

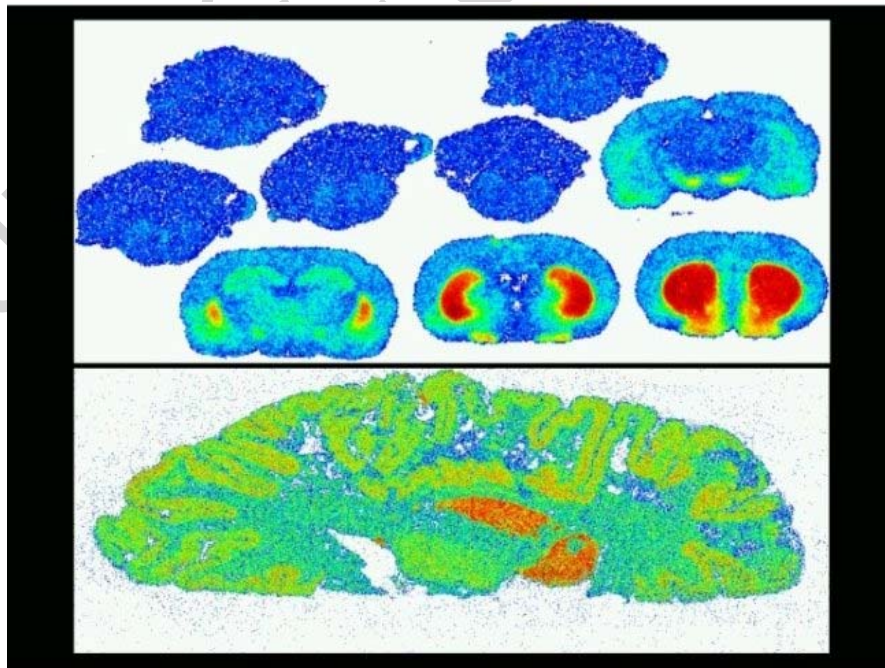


Figure 2. Examples of *ex vivo* imaging of mouse (upper panel) and *in vitro* imaging of human brain (lower panel) using a phosphoimaging system

Special devices that can directly image positron decay in thin tissue slices have also been designed. With these phosphoimagers spatial differences in tissue radioactivity concentration can be detected with a very high spatial resolution of 25 μm . The tracer is injected into a living animal and after a certain time the animal is put down, its organs sliced, and subsequently imaged *ex vivo*. In parallel with the classical autoradiography technique, *in vitro* imaging is feasible as well (see Figure 2).

2. Radiochemistry

The rapid and efficient labeling of organic molecules is a very special challenge. As molecules can be labeled to very high specific radioactivity, an intravenous injection of less than one microgram is often sufficient to perform a PET study. Thus “tracer doses,” that is, doses without any pharmacological effects, can be used.

Useful radionuclides for this purpose are carbon-11, nitrogen-13, oxygen-15, and fluorine-18. Because of the short half-lives of these radionuclides, the radioactivity production must occur on site with a small cyclotron. Carbon-11 is especially useful as almost every compound of living systems contains carbon. The rationale for using fluorine-18 is that in many molecules a hydrogen atom or a hydroxyl group can be substituted for a fluorine without altering its behavior in the human body. The short half-lives of nitrogen-13 and oxygen-15 limit the applications in radiochemical synthesis, but both nuclides appear as perfusion agents in the form of nitrogen-13-ammonia ($[^{13}\text{N}]\text{NH}_3$) and oxygen-15-water ($[^{15}\text{O}]\text{H}_2\text{O}$).

3. Drug Development, Radiolabeled Drugs, and PET

PET holds great promise in all phases of drug development ranging from the initial discovery of therapeutic targets to the fine-tuning of pharmaceutical formulations. As a multidisciplinary clinical research tool, PET can provide unique information on the distribution and properties of drug target molecules in the living organism, about pathological changes in biochemical and physiological processes in various disease states, and their responses to treatment, as well as about drug disposition. PET can be used to assess directly the pharmacokinetics and pharmacodynamics of new drugs, both in laboratory animals and in humans.

3.1. Pharmacodynamic Studies

As a functional research tool PET can be the method of choice to study pharmacological effects of new drugs. Physiological and pharmacological phenomena and biological correlates can be estimated *in vivo* by mathematical modeling of the tissue and plasma time-activity curves obtained through dynamic imaging and blood sampling. PET is currently the only technique that permits noninvasive quantification of regional tissue perfusion, glucose and fatty acid utilization, protein synthesis, and cell proliferation rate, as well as oxygen consumption in absolute terms. At best PET can be used to verify the anticipated mechanism of action (proof of concept) of a drug candidate in humans. Several methods are currently available to study the ligand–receptor interactions of new drugs in the living human brain. We can, for example, assess how an unlabeled study drug inhibits specific binding of a model PET-ligand with known receptor affinity. This

approach enables the measurement of receptor occupancy (i.e. the percentage of target receptors occupied) as a function of dose or concentration. Such knowledge can be extremely useful in the optimal design of clinical phase II and III studies. In oncology PET is used, in turn, to measure the effectiveness of new anticancer agents and to optimize therapy protocols.

3.2. Pharmacokinetic Studies

For pharmacokinetic studies the drug itself has to be labeled. Because “tracer doses” (i.e., doses without any pharmacological effects) can be used, PET studies can be carried out even before the drug enters the actual clinical phase of drug development. The information that can be obtained at an early stage includes, for example, metabolism of the compound, penetration through the blood–brain barrier and drug disposition in general, receptor kinetics, receptor specificity, and potential organ toxicity. This represents a major advantage because at present the selection of potential new drugs is commonly based on trial and error in the clinical phase of development. PET studies are relatively expensive, but can be highly cost effective if correctly applied in modern drug development.

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Bibliography

Bomanji J.B., Costa D.C., and Ell P.J. (2001). Clinical role of positron emission tomography in oncology. *Lancet Oncology* **2**, 157–164. [Up-to-date review on current applications of PET in oncology, covering all major recent published peer-reviewed data and meta-analyses.]

Iacoboni M., Baron J.C., Frackowiak R.S., Mazziotta J.C., and Lenzi G.L. (1999). Emission tomography contribution to clinical neurology. *Clinical Neurophysiology* **110**, 2–23. [A review of tomographic imaging in neurology.]

Phelps M.E. (2000). Positron emission tomography provides molecular imaging of biological processes. *Proceedings of the National Academy of Sciences* **97**, 9226–9233. [An excellent review about PET and molecular imaging.]

Reske S.N. and Kotzerke J. (2001). FDG-PET for clinical use. Results of the 3rd German Interdisciplinary Consensus Conference, Onko-PET III, July 21 and September 19, 2000. *European Journal of Nuclear Medicine* **28**, 1707–1723. [An excellent compendium of all oncologic literature on FDG-PET showing disease site oriented recommendations of indications with scientific proof of clinical impact.]

Biographical Sketches

Juhani Knuuti was born in Finland on April 8, 1960. Since 1992 he has been Professor and Director of the Turku PET Center, Turku University Central Hospital, and a consultant in the Turku Heart Center. He has been a consultant at the Department of Nuclear Medicine, Turku University Central Hospital since 1996.

He studied at the University of Turku from 1979 to 1985, when he was awarded his M.D, and took his Ph.D. in 1993. He has specialist degrees in Clinical Physiology, 1991; Nuclear Medicine, 1993; Docent (Senior Lecturer), Clinical Physiology and Nuclear Medicine, 1996.

He served as a fellow in the Department of Medicine, Turku University Central Hospital, December 1988–May 1989; the Department of Clinical Physiology, Turku University Central Hospital, May 1989–September 1990; the Department of Nuclear Medicine, Turku University Central Hospital, September 1990–January 1991. In March 1991 he became a junior researcher at the Academy of Finland. He was a consultant in Nuclear Medicine, Turku University Central Hospital, April 1991–December 1995; and at the Cyclotron-PET Center, Turku University Central Hospital, April 1991–December 1995.

He is a member of the Finnish Medical Association, Finnish Society of Clinical Physiology, Finnish Society of Nuclear Medicine, Finnish Society of Cardiology, European Society of Nuclear Medicine, Society of Nuclear Cardiology, Scientific Board, Turku PET Center, European Society of Cardiology, Cardiovascular Committee of European Society of Nuclear Medicine; he is a Nucleus Member of the Working Group of Nuclear Cardiology. He was a member of the Scientific Committee of European Society of Cardiology, 1996–1999 and in 2002 and of the International Faculty Council (Conference Committee), 2nd International Conference of Nuclear Cardiology, 1995. He has been Chairman of the Finnish Society of Nuclear Medicine since 2002.

He was awarded the Cardiovascular Council Young Investigator Award by The Society of Nuclear Medicine, 1993; the Young Investigator Award for the Best Thesis in 1994 by Turunmaan Duodecim-Seura; Young Investigators Award by the International Society for Heart Research, 1994; Poster Award, 1, Price, International Society for Heart Research, 1994; Best of Country or Region Award, 3rd International Conference of Nuclear Cardiology, 1997.

He has published approximately 100 original publications in international peer-reviewed journals, and supervised of nine finished doctoral theses between 1996 and 2001. His main lines of research can be summarized as follows: (i) the determinants of cardiac and skeletal substrate utilization in vivo; (ii) the assessment of myocardial viability and substrate metabolism in the hibernating myocardium; (iii) myocardial oxygen consumption and sympathetic innervation in heart failure; (iv) coronary and peripheral artery reactivity and endothelial function.

Heikki R.I. Minn was born in Turku, Finland, in 1956. He is married, with two children.

He graduated from Turun Normaalikoulu, Finland, in 1975 and took his Licentiate of Medicine (M.D.) in 1984 at the University of Turku where, in 1990, he was awarded his Doctor of Medicine (Ph.D.). His specialist competency: is Oncology (Certified, University of Turku), 1991; he became Docent in Clinical Oncology at the University of Turku, in 1995.

His professional experience includes work as: General Practitioner (various positions), Primary Health Care, Finland, 1983–1984; Oncology Resident, University of Turku, Finland, 1984–1986; Junior Research Fellow, Academy of Finland, 1987; Physician at the Military Hospital of Turku, Finland, 1988; Oncology Resident, University of Turku, Finland, 1989–1990; Nuclear Medicine Fellow, Department of Nuclear Medicine, University of Turku, Finland, 1991; Diagnostic Radiology Resident, Keski-Pohjanmaa Central Hospital, Kokkola, Finland, 1991; Specialist Physician, Department of Oncology and Radiotherapy, University of Turku, Finland, 1992–1993; Visiting Instructor, the University of Michigan, Division of Nuclear Medicine, Ann Arbor, MI, USA, 1993–1994; Specialist Physician, Department of Oncology and Radiotherapy, University of Turku, Finland, 1994–1996; Acting Professor, Department of Oncology and Radiotherapy, University of Turku, Finland, 1997; Specialist Physician, Department of Oncology and Radiotherapy, University of Turku, Finland, 1998–1999; Specialist Physician, Turku PET Center, University of Turku, Finland, 1999–present.

Dr. Minn is a member of: the Finnish Oncological Society, Finnish Society of Nuclear Medicine EEC Task Force for PET Studies in Oncology, Scandinavian Society for Head and Neck Oncology (Board

Member), European Society for Therapeutic Radiology and Oncology, Consultant Physician for Radiotherapy at Finnish Radiation and Nuclear Safety Authority (STUK), and the American Society for Therapeutic Radiation and Oncology (International Member).

He has published approximately 60 original publications in international peer-reviewed journals on subjects including head and neck cancer, CNS tumors, radiation oncology, and nuclear medicine, with special emphasis on positron emission tomography (PET).

Juha O. Rinne was born in Finland in 1960, and is married, with three children.

He graduated from Turun Normaalikoulu, Finland, in 1979, and in 1985 gained his Licentiate of Medicine (MD), University of Turku, Finland, where he became Doctor of Medicine (Ph.D.) in 1987. He became Docent in Experimental Neurology in 1989. His specialist competency is Neurology (Certified, University of Turku, 1993). He became Docent in Clinical Neurology at the University of Turku in 1995, and was appointed Professor at the Turku PET Center in 1999.

His postgraduate medical or scientific training and research experience includes: Research Fellow, University Department of Clinical Neurology, Institute of Neurology, the National Hospital for Neurology and Neurosurgery Queen Square, London, UK, 1992–1993; Research Fellow, MRC Cyclotron Unit, Hammersmith Hospital, London, UK, 1992–1993. His experience in medical practice includes: acting as clinical medical assistant at the Departments of Internal Medicine, Surgery and Neurology, University of Turku, 1977–1985; General Practitioner and Assistant Physician at the Departments of Internal Medicine and Geriatrics, City Hospital of Turku, 1985–1989; Resident of Neurology, Department of Neurology, University Central Hospital of Turku, 1989–1993; Specialist of Neurology (Consultant), Department of Neurology, University Central Hospital of Turku, 1993–2001; Specialist of Neurology (Consultant), Lääkärikeskus Mehiläinen, Turku, 1998–present.

Since 1991 he has served as ad hoc reviewer for *Brain Research*, *European Journal of Neurology*, *Journal of Neurology*, *Journal of Neurology Neurosurgery and Psychiatry*, *Neurology*, *Movement Disorders*, *J Cerebral Blood Flow and Metabolism*, *Annals Neurology*. He has also served as reviewer of doctoral theses at the University of Kuopio, 1990, 1994, 1995, 1998; University of Helsinki, 1998; Docentship, University of Kuopio, 1992, 1996, 1997 (twice), University of Tampere, 1996. He acted as opponent in an academic dissertation at the University of Kuopio, 1992 (twice), 1993, 1994, and 1995, and at the University of Helsinki, 1998. He has acted as supervisor for six completed academic theses and for three in progress.

He has been a member of: the Duodecim (Finnish College of Physicians), 1982; Brain Research Society of Finland, 1985; Finnish Neurological Association, 1988; Finnish Gerontological Association, 1988; Finnish Alzheimer Society, 1988; World Federation of Neurology: Research Group on Dementias, 1991; International Society of Cerebral Blood Flow and Metabolism, 1991; American Academy of Neurology, 1992; Finnish Alzheimer Research Society, 1997.

He has published approximately 150 original publications in international peer-reviewed journals on neuropathological and neurochemical aspects of aging, dementia (especially Alzheimer's disease), and Parkinson's, with special emphasis on positron emission tomography (PET).