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Role of Positron Emission Tomography in Various Aspects of Pharmacy

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Researchers at various centres throughout the world are applying positron emission tomography (PET) to the study of *in vivo* metabolic process. PET is an imaging modality, which is a noninvasive diagnostic technique, in which radioactive tracers are used to measure the anatomical distribution and kinetics of specific biochemical processes. This is a quantitative approach towards the measurement of pharmacokinetics of labelled drugs and assessment of their effect on the metabolism by using radio pharmaceutical labelled with positron emitting radionuclides as ^{11}C, ^{13}N, ^{15}O and ^{18}F. Since the dose required is very little, so PET provides cost effective predictive toxicology data and information on the metabolism and mode of action of drugs before the drug is in phase I. This paper presents a review to the applications of PET, especially in the field of drug design and development.

Key Words: Positron emission tomography, Radionuclides.

INTRODUCTION

The basis for non-invasive *in vivo* measurements with positron emission tomography (PET) lies in the use of physiologically active compounds labelled with positron emitting isotopes. PET is a recent development in the study of pharmacokinetics and pharmacodynamics of drugs in man and it can be used to obtain new information about novel and established drugs[1–3].

PET mainly includes short-lived positron emitting radiopharmaceuticals. Positron emitters are neutron deficient compared to their stable counterparts. Decay occurs by spontaneous conversion of a proton to a neutron, accompanied by release of a positron (positive electron), *e.g.*, F-18, O-18 (proton 8, neutrons 10) releasing a positron[4, 5]. The radionuclides used most widely are ^{11}C ($t_{1/2}$ = 20 min), ^{13}N ($t_{1/2}$ = 10 min), ^{15}O ($t_{1/2}$ = 2 min), ^{18}F ($t_{1/2}$ = 110 min)[5]. Carbon, oxygen and nitrogen are the elements of life and are used in the formation of every molecule of biological importance. Due to the short half-lives the radionuclides have to be produced in-house with a cyclotron but ^{18}F is an exception, which has a half-life of nearly 2 h. For labelling of complex structures rapid radiochemical production methods must be available among the above mentioned radionuclides.

Since almost every compound in living systems contains carbon, so ^{11}C has more potential than ^{18}F in drug development[6, 7].

PET Scan

The positrons, which are ejected, travel less than 3 mm before encountering an electron and undergoing antimatter-matter annihilation. The annihilation process generates two 511-keV gamma rays that radiate in opposite directions. These body-penetrating gamma rays are then detected by a circular array of scintillation crystals connected such that opposing crystals are grouped in coincidence circuits. In this individual positron decay, events can be localized along a geometric chord of the detector array[8–10]. The computer catches several million coincidences during 1–15 min of scan interval for subsequent reconstruction into tomographic images displaying the spatial arrangements of radioactivity. These images along with blood radioactivity data are collected prior to and during the scan and are further processed with *ad hoc* biomathematical models yielding a quantitative measurement of the dynamic process under study[11, 12]. For detection of radiation positron cameras are available in which the basic detector is a BGO detector supported by 4 photomultiplier tubes (PMT). The detector blocks form a ring and 4 of these rings can be added to get an axial field of view of approximately 15–16 cm. These cameras are designed for small animals because they have a spatial resolution of 2 mm[13, 14]. Positron cameras are able to measure the radioactivity in absolute terms. These cameras generally include coincidence technique, which allows correction of the attenuation of radiation inside the body. This correction is based upon making of an individual transmission image.

The principle of the PET technique is demonstrated in Fig. 1. Positron emitting radionuclides disintegrate and emit positrons (positively charged electrons, β^+), that interact with the corresponding antiparticle, an electron (β^-) after travelling in tissue for 1–2 mm[13]. The mass of the two particles is converted to gamma radiation (annihilation) and two 511 keV protons are emitted simultaneously in opposite directions. A ring of scintillation detectors placed around the subject detects the rays emitted externally. The two gamma signals have to be registered by two coincidence-coupled detectors within a time window to be counted as originating from the same disintegration. The last generation of PET-systems is used for data acquisition and image reconstruction of 47 slices in the 3D mode with a spatial resolution of 3–4 mm[14, 15].

Several PET radiopharmaceuticals are nowadays used as standard tools for the investigation of various disease states and control of treatment effect with drugs, *e.g.*,

- 2-[^{18}F]-Fluoro-2-deoxyglucose ([^{18}F] FDG) is the most frequently used tracer in the measurement of glucose metabolism in tumours, heart and especially brain in various disease conditions[16].
- 1-[^{11}C] Acetate, which enters the Krebs tricarboxllic acid cycle at the last possible step by binding to coenzyme A, can be used as a tracer to reflect the oxygen consumption in the heart[17].
- [^{13}N] Ammonia is a precursor that can be incorporated into bimolecular.

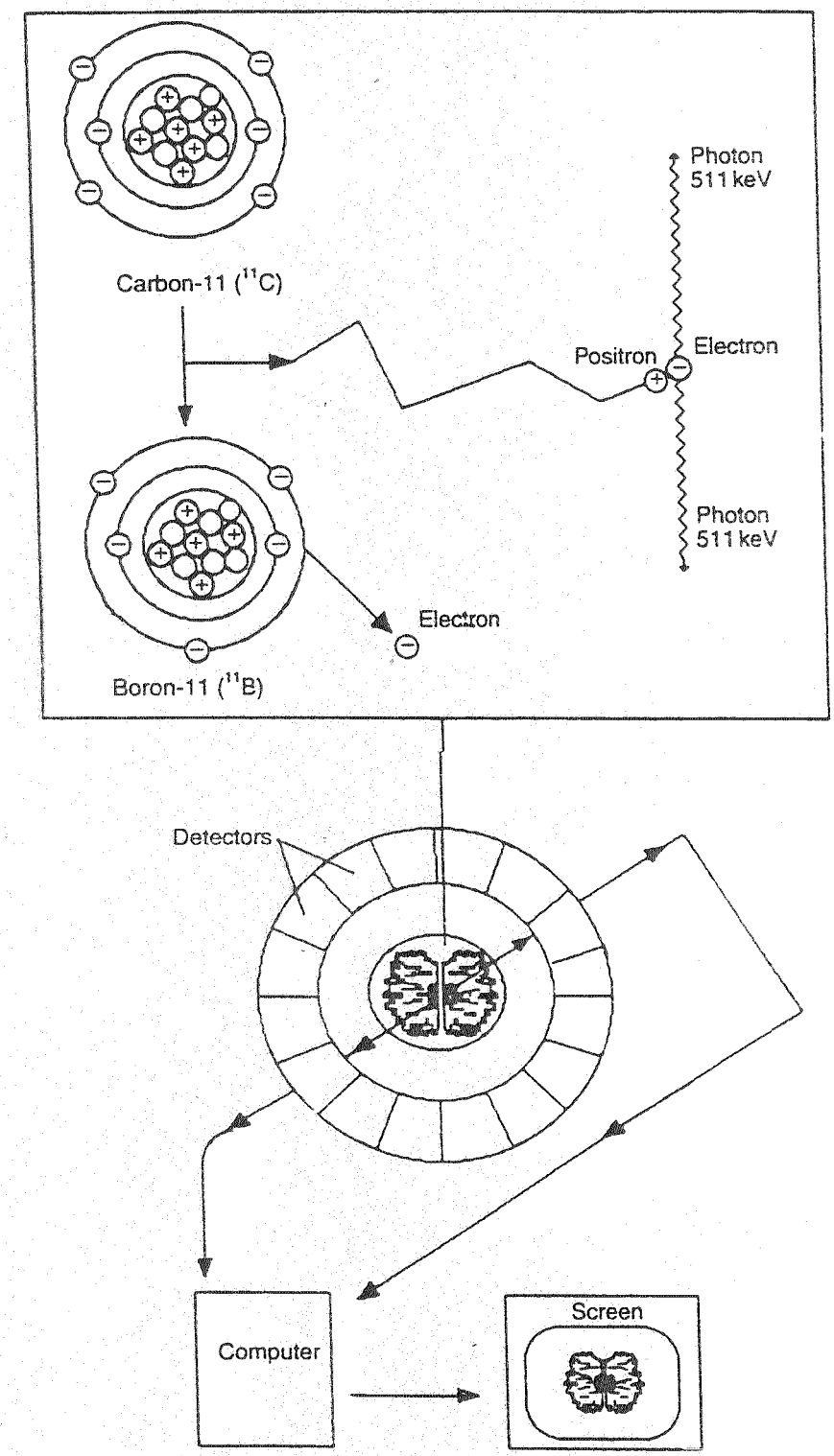

Fig. 1. The positron-emitting radionuclide ^{11}C decays to form a positron, which annihilates with an electron. The resulting gamma energy, two photons travelling in opposite directions, can be detected externally by a ring of scintillation detectors placed around the subject in the PET camera.

However it is a readily diffusible tracer and it enters tissues and metabolic processes which will alter the regional blood flow[18].

- L-[^{11}C] Methionine reflects the amino acid utilization, *i.e.*, transport, protein synthesis, transmethylation and other metabolic processes[18].
- *n*-[^{15}O] Butanol and [^{15}O]H_2O are used to study blood flow in the brain and other organs[19].
- Carbonl [^{11}C] WAY-100635 is a selective antagonist for the serotonin 5-HT_{1A} receptors, which is used to measure receptor density[20].

Various other PET radio ligands have been developed for the presynaptic norepinephrine uptake system in the heart. Most of them are, however, analogs labelled with either ^{18}F or ^{76}Br[20, 21].

Comparison of PET with other imaging modalities

The most common imaging technique used in medicine is X-rays. Holding the subject of interest between the X-ray tube and a photographic plate in a simpler form generates a density projection[22]. The advanced form is CT scan or computed tomography which gives transverse section image, a kind of density map. Although extraction of the exact density will not be possible because of the large difference in density of the bones and the tissue, the bones can be visualized perfectly while small differences in tissue density will be more difficult to detect[23–25]. The use of contrast agents, *e.g.*, fluids with high densities and high atomic numbers can change the difference in density and by this the interpretation of the images.

The nuclear magnetic resonance (NMR) is generally used to visualize proton in the human body. The strength of the NMR signal is proportional to the difference in population of the spin-up and spin-down state. Under normal conditions at room temperature the ratio between spin-up and spin-down is rather close to unity. For this reason, the NMR technique is insensitive but it is successful because of high water concentration in the human body. NMR gives information on the structure of molecules as is done in chemistry. Proton spectroscopy is possible in the human body but limited to the brain[26–33].

The use of radionuclides incorporated into different molecular structures gives functional imaging. In this, the chemical structure of the radiopharmaceutical and metabolism in the human body gives the fate of the molecule *in-vivo*. The PET technique is superior and is the normally accepted method for measuring the rcBF (regional cerebral blood flow) in man[34, 35]. Since PET supplies functional information, the combination with PET and MRI yields functional anatomy.

Applications

After intravenous injection/inhalation of the labelled drug the distribution of radioactivity in different organs and tissues is measured quantitatively. By changing the labelling of positron in the molecule detailed new information can be obtained on the mode of action. Studies with radio-labelled established drugs have the advantage that the toxicity profile is available[36, 37]. Early information can be obtained on the metabolism of the blood-brain barrier penetration, the

receptor kinetics and specificity of the compound in humans. Radiotracer methodologies are extremely useful to study with high sensitivity the metabolic consequences of gene expression or gene defects. Especially the contribution of PET is considered important to study noninvasively the genomic metabolism relationship *in vivo*[38–41].

In vivo knowledge of the receptor density and functionality is important to estimate the sensitivity of breast and prostate tumours to hormonal therapy. This PET application is of direct clinical value in radiotherapy to monitor radio sensitivity of tumours[42]. Multi drug resistance (MDR) is one of the molecular biology aspects of tumours. MDR involves various mechanisms. Understanding of such mechanisms may contribute to understanding of the mode of action of the drug. A possibility to study MDR is by labelling the chemotherapeutic agents with a positron emitting radionuclide and monitoring the kinetics of radioactivity in the tumour *in vivo* [^{18}F] 2-fluoro-2-dioxyglucose (FDG). FDG/PET provides quantitative estimates of glucose utilization. FDG is transported between blood and brain and both are excellent substrate analogues for hexokinase, the first enzyme of the glycolytic pathway. The absence of a hydroxyl group at c-2 in FDG, however, blocks subsequent transformation, thereby metabolically trapping FDG-6-phosphate within cells. Neurons consume ATP when firing; so active areas of brain require more energy than inactive areas. Since the brain depends exclusively on blood glucose as an energy source, rcMRglu (regional cerebral glucose metabolic rate) proportional to the regional accumulation of FDG radioactivity, is a sensitive index of brain function. FDG/PET provides a general means of studying neuropsychological abnormalities by comparing differences in rCMRglu between normal and patient populations[43–49].

Modelling metabolic processes in heart is more complex than for the brain because the heart can draw energy from various sources, *e.g.*, carbohydrates, fatty acids and lactate. Nevertheless, PET studies are proving useful to distinguish healthy, ischemic (blood supply insufficient) and infarcted tissue[50].

PET in relation with synthesis

Developmental chemistry using small quantities of radioactivity is often performed semi-remotely in warm cells, which are conventional fume hoods outfitted with appropriate shielding to make them suitable for testing various reactions safely and easily. Another special consideration in planning synthesis with positron emitters is stoichiometry. Some biochemical specially neurotransmitters are present *in vivo* at such low concentration that chemists synthesizing labelled analogues must also be concerned with unintentional contamination of the cyclotron produced radioisotope by stable isotope[51–53].

Gene Therapy with PET

Advancements in the field of genetic engineering and molecular biology have also opened the door to therapy by transferring genes into cells. Herpes simplex virus thymidine kinase (HSV-tk) is a promising target in this regard. In order to make cancer treatment with HSV-tk more successful, it is required to optimize the gene delivery system. PET can give unique information about the extent and

location of gene expression provided an appropriate reporter gene is included in the therapeutic cassette and adequate radiopharmaceuticals for imaging are developed. Imaging based on labelled ganciclovir (indicating HSV-tk enzyme activity), ganciclovir related drugs or thymidine analogues might allow monitoring of HSV-tk activity *in vivo* in man[54, 55].

Regulatory aspects

PET radio pharmaceuticals are produced in the non-carrier added range at the amounts that have to be administered for a useful PET signal; no pharmacological effects or toxicity is expected; however, one has to be cautious. The safety of the labelled compound can be based on an abnormal toxicitiy test as described in the European Pharmacopoeia[55, 56].

Conclusion

Positron emission tomography offers unique opportunities for medical researchers to understand the human physiology, to study the chemical basis of neuropsychological disease and for the evaluation of efficacy and specificity of a drug at molecular level. PET offers various possibilities to study physiology, molecular biology, metabolism pharmacology and pharmacodynamics in humans *in vivo*. PET challenges the chemists to utilize the synthetic reactions.

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