Biometals (2009) 22:393–399
DOI 10.1007/s10534-008-9181-4

Imaging atoms in medicine

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Received: 12 September 2008 / Accepted: 14 November 2008 / Published online: 2 December 2008

Abstract The innovations in science and technology have allowed researchers to look inside the human body. In some cases, like MRI, the protons present in the body generate enough signal for an image. However, the employ of certain atoms, metallic or non-metallic, enable detection through different imaging techniques (computed tomography, nuclear imaging, ultrasound or optical imaging), and improve the quality of the images. Here we discuss the different imaging atoms used depending on the imaging technique and the new possible imaging atoms for medical applications.

Keywords Atoms · MRI · CT · Nuclear imaging · US · OI

Introduction

The discovery of X-rays in 1895 by Röntgen opened up the doors to the clinicians to look inside the body. X-rays was the first imaging technique developed and over the course of the years, new ones more or less invasive have been built up by scientists. Among them we can cite magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), ultrasound (US), and optical imaging (OI). These techniques play an important role as diagnostic tools for medical examinations.

All the techniques make use of contrast agents (CAs) to improve the quality of the images of the different regions of interest in the body. There are a huge variety of elements that can be used for the different imaging modalities as contrast agents. In order to group them, the elements will be categorized depending on the imaging modality employed. Metal ions play an important role in medicine (Thompson and Orvig 2003) and a large number of them are involved in the formulations of the different solutions employed by medical doctors for imaging examinations. Non-metallic elements and even noble gases have also found an important task in medicine as imaging elements.

Magnetic resonance imaging

Since Lauterbur reported that, with superimposition of linear field gradients to the static magnetic field in an NMR experiment it is possible to obtain projections of an object, MRI has become a routine diagnostic tool in clinical medicine. The physical basis of this technique relies on the relaxation rate of the protons in the body. It is noninvasive, has a

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superb spatial resolution, and yields anatomical information. Contrast agents are chemical substances that further enhance the contrast of the images. They are paramagnetic, superparamagnetic or ferromagnetic materials that shorten the relaxation times of bulk water protons. Contrast agents can be classified whether they alter $1/T_1$ more than $1/T_2$ or whether the increase is mainly observed in $1/T_2$.

The majority of the contrast agents for intravenous administration are based on gadolinium ions chelated by a polyaminocarboxylate ligand either macrocyclic or open chain that form thermodynamically stable and kinetically inert complexes (Caravan et al. 1999). Gadolinium based CAs usually injected for MRI procedures are non-specific for a particular pathology. One approved manganese imaging agent for clinical use is a solution of Mn(II) chelate of dipyridoxal diphosphate (DPDP) that is utilized as a hepatocyte specific MRI contrast agent (Merbach and Tóth 2001).

Another type of imaging agents used for MRI is superparamagnetic iron oxide nanoparticles. These agents are surrounded by a polymer layer and produce a darkening of the contrast enhanced tissue due to the shortening in T_2. These nanoparticles are taken up by the monocyte–macrophage system, which make them suitable as marker of inflammatory and degenerative disorders (Corot et al. 2006). ^{23}Na imaging represents another element with potential sensitive and noninvasive means of monitoring sodium concentration within tissues. With ^{23}Na MR it is possible to characterize myocardial infarction, imaging of the kidney, cartilage, and brain (Granot 1988).

Metallic atoms are not the only elements employed for MRI imaging. Non-radioactive noble gases such ^{3}He and ^{129}Xe with a nuclear spin 1/2 can be hyperpolarized by a laser light. The hyperpolarized gases are administered as inhalative contrast agents allowing for imaging of the airways and airspaces (Fig. 1) (Kauczor et al. 1998).

Computed tomography

Computed tomography is a radiographic technique used to produce cross-sectional images of the human body after an X-ray beam passes through a patient. A major breakthrough was achieved in late 1990 with the introduction of multislice CT scanners (MSCT). This technology allows to shorter the acquisition time, spatial and temporal resolution, reduction of helical artifacts. CT is sensitive to differences in tissue densities and can differentiate a variety of soft tissue without the aid of contrast agents. However, contrast agents play an important role in many CT examinations. Contrast agent research started the same year Röntgen discovered X-rays. Since X-rays are not sufficiently absorbed by soft tissue, elements with high atomic numbers such iodine, barium, bismuth, and lead were soon discovered to be useful as contrast enhancers. Today, more than twenty millions of iodinated X-rays contrast agents are employed annually in the United States for computed tomography and angiographic applications. These contrast agents are based on modifications of the

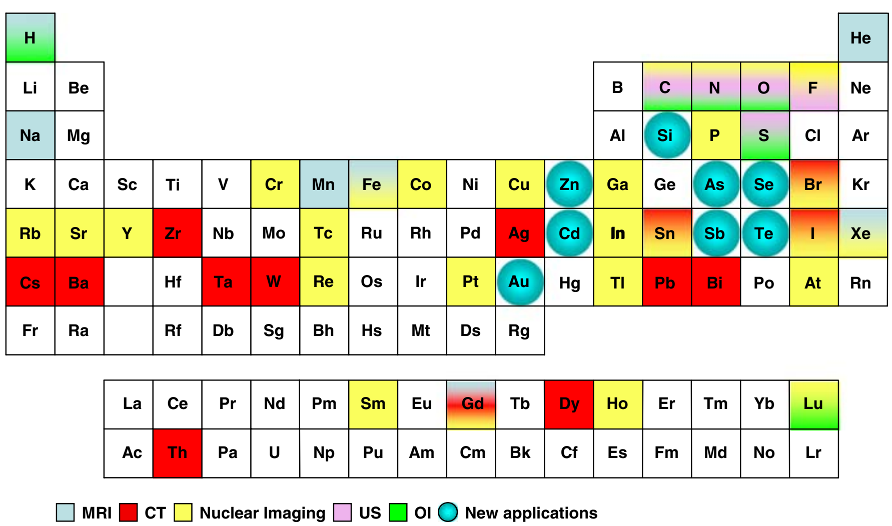

Fig. 1 Periodic table highlighting the elements used for the different imaging modalities employed for diagnosis in humans and those that could be used

triiodinated benzene ring (Singh and Daftary 2008). Barium sulfate has been used for nearly a century, its suspension in water is the universal contrast medium used for examinations of the upper gastrointestinal tract (Erturk et al. 2008).

Although the later elements are extensively used for imaging procedures other metals mainly used in early years of X-ray examinations have been employed. At the beginning of 1900 a colloidal silver preparation was used in urinary tract radiography. Bismuth salts were perhaps the first X-rays contrast agents for general use in human patients. Other elements such as Cs, Th, Sn, Zr, Ta, W were employed for bronchography or other imaging examinations but were discarded due to several problems such as toxicity, did not improved the results from the previous contrast agents, radioactive emission, long term body retention (Yu and Watson 1999). Bromine has also been used in patients as contrast agents for liver and spleen uptake, although several adverse effects were described such as fever, lower back pain, and malaise (Behan et al. 1993).

Gadolinium chelates used as contrast agents for MRI procedures were serendipitously found as X-ray contrast enhancers. In cases were patients have contraindications for iodine exposition, gadolinium has been considered to be a safe alternative to standard iodinated contrast medium. Nevertheless, further studies in order to evaluate possible life-threatening side effects and complications have to be considered. Disprosium (Dy) was also tested in humans as a chelate with an open chain polyamino-carboxylate (EOB-DTPA) resulting in a time window of 90 min for liver lesions while iodine compounds just have 20–40 s window (Yu and Watson 1999).

Nuclear imaging

Positron emission tomography (PET) is a non-invasive nuclear imaging technique that uses short-lived positron ($\beta+$) emission isotopes. When the positron is emitted travels a short distance before it is annihilated by an electron. This process release an energy in the form of two 511 keV γ-photons at 180° to each other. If those photons are detected at the same time, then their origin will lie on a line joining the two detectors. By taking a number of views, a series of intersecting lines is obtained which allows the point of origin to be identified in three dimensions. PET has become the dominant imaging method in the field of nuclear medicine. It uses tracers labeled with radionuclides which form stable covalent bonds to carbon atoms allowing the study of physiology, molecular biology, energy metabolism, drug-receptor interaction and the fate of the tracer in living tissues. It combines a relatively high resolution with a remarkably high sensitivity (up to 10^{-12} mol l^{-1}). Single photon emission computed tomography (SPECT) uses γ-emitting radionuclides in the energy range of 75–360 keV that provide superior information to conventional planar imaging, it suffers from poor spatial, contrast, and temporal resolutions compared with PET. Its use is usually confined to specific anatomical sites such as the brain, chest, or abdomen.

The radionuclides can be classified in two categories: (1) non-metallic and (2) metallic radioisotopes (Hamoudeh et al. 2008). Among the non-metallic radioisotopes we can find ^{15}O, ^{13}N, ^{11}C, ^{18}F, ^{76}Br (Bruehlmeier et al. 2003), $^{123, 124, 125, 131}$I, and ^{133}Xe (Shinya et al. 2008). By far, [2-^{18}F] fluorodeoxyglucose ([^{18}F]-FDG) the most widely studied tracer is used for the assessment of glucose metabolism in the heart and in the brain, it also has been used in oncology to image tumors. Metallic radionuclides comprise a large number of radioelements. $^{66, 67, 68}$Ga (^{68}Ga-citrate has been used to quantify pulmonary vascular permeability); $^{60, 61, 62, 64}$Cu (^{62}Cu-ATMS (Cu(II)-diacetyl-*bis*(N^4-methylthiosemicarbazone)) has been shown to be selectively trapped in hypoxic tissue in both myocardium and tumors) (Anderson and Welch 1999); ^{99m}Tc (^{99m}Tc-sestamibi is employed for myocardial perfusion imaging) (Liu and Edwards 1999); ^{86}Y, (^{86}Y-DOTA-Octreotide form has been used for tumor imaging (Helisch et al. 2004)); ^{111}In (^{111}In-DTPA-Octreotide is used for the diagnosis of somatostatin receptor positive tumors) and cobalt radionuclides (^{55}Co, ^{57}Co are able to visualize inflammatory lesions, probably by means of the final common pathway of Ca^{2+} homeostasis disturbance in both neuronal degeneration and inflammation) (Anderson and Welch 1999). ^{52}Fe has been used to radiolabel blood cellular elements because offers a higher sensitivity and resolution than conventional imaging and has shown uptake in organs like the liver, brain or bone marrow (Ellis and Sharma 1999). There is a plethora of other radionuclides that also have been used for different medical procedures in patients: ^{82}Rb, ^{201}Tl, ^{188}Re, ^{153}Gd, ^{153}Sm, ^{89}Sr, ^{32}P, ^{117m}Sn, ^{166}Ho, ^{177}Lu, ^{191}Pt, ^{211}At, ^{51}Cr (Knesaurek et al. 2007; Yu et al. 2008; Xiong and Chen 2008; Jacobs et al. 2004; Maini et al. 2004; Cipriani et al. 1997; Siegel and Khan 1996; Krishnamurthy et al. 1997; Breitz et al. 2006; Wehrmann et al. 2007; Areberg et al. 1999; Zalutsky et al. 2008; Arnello et al. 1999).

Ultrasound

Ultrasound is an extensively used diagnostic medical imaging modality. It is versatile, non-invasive, and relatively low in cost and risk. Ultrasound images, however, do not have a very sharp contrast and sometimes the area being imaged is buried and shadowed by tissue. Nevertheless, the quality of the images can be improved with the help of ultrasound contrast agents. They were proposed nearly three decades ago when it was accidentally discovered that air bubbles could be detected in the blood stream after injections of agitated aqueous solutions (Sboros 2008). Since that, several generations of US contrast agents have appeared. The first generation of ultrasound contrast agents was based on air or gas suspended in liquid, which were unstable in the blood stream. The second generation of contrasts contained encapsulated ultrasound microbubbles which increased the stability in the body for longer periods. The third generation contains perfluorocarbon gas ($CF_3(CF_2)_nCF_3$, $n = 1–4$) (Fritz et al. 1997) or sulfur hexafluoride (SF_6) (Schneider et al. 1995) rather than air or N_2 which results in a longer life of the contrast agents within the circulatory system.

The acoustic backscatter of microbubbles may be orders of magnitude greater than the backscatter of blood and the surrounding tissues and organs. The contrast agents alone or incorporating ligands on the surface for selective imaging have been used to image inflammation, tumor angiogenesis, transplant rejection or ischemia-reperfusion injury (Klibanov et al. 2006).

Optical imaging

Optical imaging is an emerging modality in the growing field of biomedical diagnostic. Optical imaging encompasses different techniques which use light of the UV to the NIR spectral region to characterize tissue optical properties imparted through absorption and scattering of light, as well as emission of fluorescence. An important observation for optical diagnostic procedures relates to the fact that the penetration depth of light in living tissue strongly depends on the wavelength used. The optical window ranging from 700 to 900 nm allows the use of fluorescent dyes for novel diagnostic solutions. The attractiveness of this technique arises from the fact that fluorescent dyes can be detected at very low concentrations up to 10^{-17} mol l^{-1} (Licha and Olbrich 2005).

The only modality which is in daily and widespread routine clinical practice so far is the imaging of ocular diseases in ophthalmology. Fluorescein and indocyanine green (ICG) are established as fluorescent agents to enhance tumors, rethinopathies, or vascular disorders. Optical contrast agents have also been employed to detect breast tumors and for the imaging of the brain (Liebert et al. 2006).

5-Aminolevulinic acid (ALA) has been used to evaluate the accuracy and safety of tumors resection in fluorescence guided identification of brain tumors and tumor margings since induces the accumulation of fluorescent porphyrins (protoporphyrin IX). Lutetium motexafin, is an example of expanded porphyrin derivative which is currently used as photodynamic therapy (PDT) agent for the treatment of cancer (Fig. 2) (Licha and Olbrich 2005).

Future perspectives

The different imaging techniques presented in this paper have provided to the researchers and clinicians tools to acquire in vivo images for diagnostic purposes. Each one of these techniques possesses unique advantages and disadvantages. New contrast agents that incorporate the advantages of two or more imaging techniques, what has been coined as multimodal contrast agents, are at this time being developed. For example, the company Schering, now Bayer, has developed a hybrid new contrast agent that combines in a molecule three moieties for MRI imaging with three gadolinium ions and a moiety for CT imaging with three iodine atoms (Weinmann et al. 2005). As mentioned, the MRI contrast agents employed in clinical routine examinations lack of specificity so

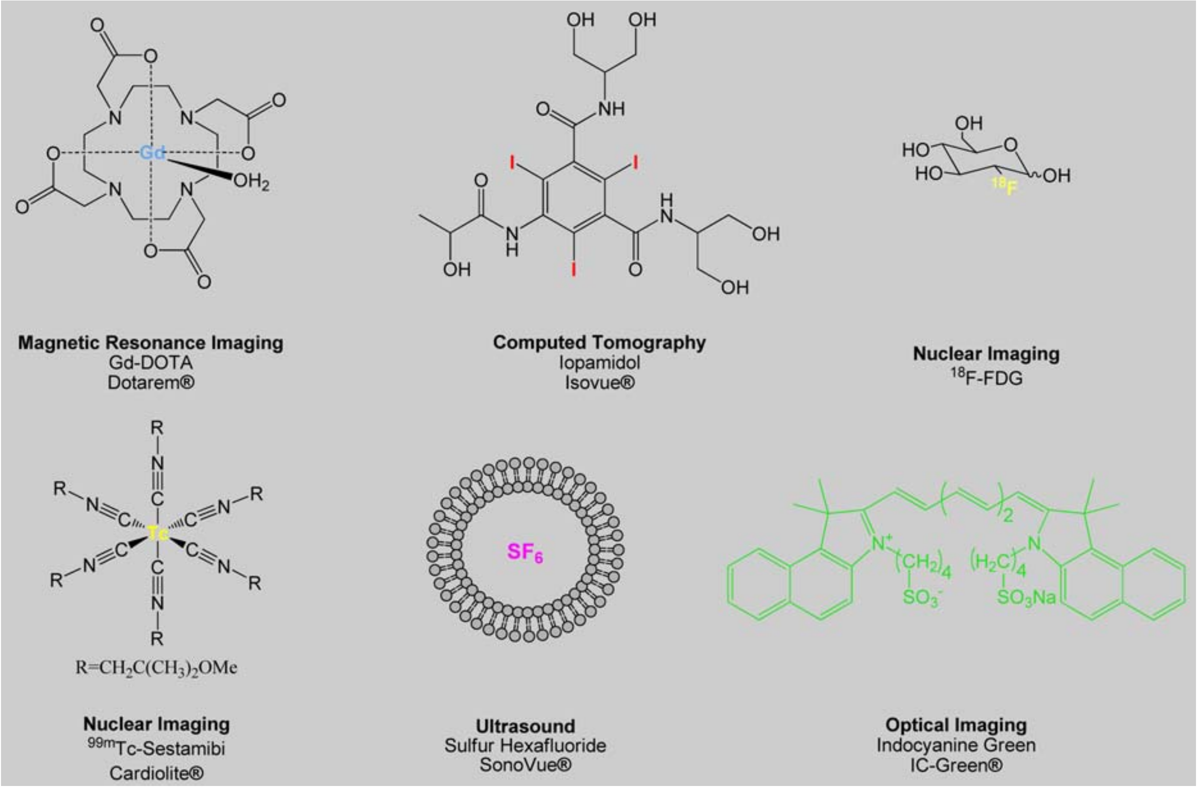

Fig. 2 Different contrast agents employed for human examinations depending on the imaging modality chosen

scientists are developing smart contrast agents selective to the tissue to be studied that provide better enhancements of the images (Caravan 2006).

Furthermore, new contrast agents based on different atoms to those presented here are under study. In this case, gold compounds (Auranofin) have being used in the management of rheumatoid arthritis. Recently, it has been reported (Hainfeld et al. 2006) on a mouse model that gold nanoparticles could be useful X-ray contrast agents since gold provides 2.7 times greater contrast per unit weight than iodine and appear to be non-toxic.

Quantum dots (QDs) have shown promising results due to their improved brightness, multicolor light depending on the size and resistance to photobleaching in optical imaging for living tissue (Michalet et al. 2005). In combination with modified phospholipids they have been used in a mouse model to highlight by MRI and optical imaging atherosclerotic lesions (Mulder et al. 2007).

Progress has accomplished new machines that in a single image combine anatomical and functional information. Nowadays, in hospitals can be found hybrid systems such PET/CT, SPECT/CT, or more recently PET/MRI, so future challenges are related to the synthesis of smart contrast agents capable to target the part of the body under examination with a high signal to noise ratio and with the ability to combine in a single molecule two or more elements suitable for different imaging technologies.

Acknowledgments M. T. A was supported by a JdlC Fellowship. J. C. F. thanks Ayuntamiento de Valencia for the Carmen y Severo Ochoa Fellowship. We acknowledge financial support from Generalitat Valenciana (GV/2007/141).

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