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Importance of Chemistry in Pet-Ct Studies

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Abstract

Positron Emission Tomography - PET is an imaging technique in which the patient is given a tracer called a radiopharmaceutical, which is the union of a drug or a physiological substance with known pharmacokinetics and pharmacodynamics with a radioactive positron emitting atom. It allows us to correctly evaluate and measure relevant bodily functions: • blood flow • the use of oxygen • the metabolism of sugar (glucose). The most used radiopharmaceutical for carrying out a PET-CT study is Fluordeoxyglucose, whose full name is 2 -fluoro-2-deoxy-D-glucose, but its short form FDG is usually used.

Keywords: Positron Emission Tomography; Pharmacodynamics; Pharmacokinetics; Radiopharmaceuticals

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Radiotrazadores

Radiotracers or radiopharmaceuticals are chemical substances that, together with radioactive isotopes, are selectively incorporated in the area to be explored, allowing the study of the functioning of different organs.

All radiopharmaceuticals are usually composed of two fractions:

- **The radionuclide:** Fraction that emits the radiation that is detected by the specific instruments (Gammacámara or PET).
- **The drug:** Chemical fraction, organic or inorganic, which determines the bio distribution of the radiopharmaceutical to the target organ and its subsequent location.

Radiopharmaceuticals include diversity of physical and chemical forms: elements, inorganic salts, organic molecules, coordination compounds, particle suspension cells. The way in which they are administered to people varies according to the radiopharmaceutical used, many of them are administered orally, and many others are administered intravenously.

Characteristics of Radiotrazadores

Radiotracers have a double nature; On the one hand, the molecule has characteristics that cause it to be distributed throughout the body in a specific, but they are the radioactive isotopes emitting gamma rays that carry artificially incorporated, those that allow its detection, and therefore the demonstration of the result of the processes that cause this substance to be deposited in different locations.

The choice of the tracer is of fundamental importance since, whatever its nature, it must meet the following requirements:

- Be easily detectable in low concentrations.
- Behaving identically to the product under study.
- Can be detected easily and unambiguously.
- Do not precipitate, not be absorbed by the medium, or be removed from the system by some other mechanism.
- Injection, measurement and sampling operations should not affect the behavior of the system.
- Have good availability and acceptable cost.
- The residual concentration of the tracer at the end of the experience should be minimal.

That is why you must work with the proper chemical form for each particular problem. In the case of being a radioisotope, it must also fill requirements regarding the type and energy of the radiation emitted and the period of semi-disintegration.

What is Fluordeoxyglucose - FDG?

The most commonly used radiopharmaceutical for conducting a PET-CT study is Fluordeoxyglucose, whose full name is 2-fluoro-2-deoxy-D-glucose, but its short form FDG is usually used. It is an analog molecule of glucose used as a metabolic marker that enters the cells, tumor or not, through the different membrane receptors, follows the same metabolic pathway of glucose and is phosphorylated by hexokinase, in the presence of glucose 6-phosphatase, converting it to 18F-FDG-6 phosphate, but from this point on it does not continue and is accumulated intracellularly with greater concentration in the tumor cells. This difference in concentrations given by the higher glucose consumption and lower amount of glucose 6-phosphatase are the basis of the diagnosis. This radiopharmaceutical allows the study of the cellular metabolism of glucose and is the most used in PET thanks to its greater availability, since its half-life is 110 minutes, which allows its displacement to the different production centers.

Once administered to the patient, the FDG is incorporated into the cells being trapped, without being metabolized. This allows evaluating the glycolytic activity that is higher in neoplastic cells compared with normal cells **(Figure 1)**.

Production of the FDG

The conditions of bombardment with high-energy particles used in the medical Cyclotron (particle accelerator) to produce 18F would destroy any organic molecules such as deoxyglucose or glucose. Therefore, the isotope 18F must first be created as fluoride in the cyclotron. This can be achieved by bombardment of neon-20 with deuterons, but generally, it is carried out with proton bombardment of water enriched with 18°, which results in a synthesis reaction of 18F radioactively labeled in the form of hydrofluoric acid (HF). The rapid radioactive decay of the 18F obtained, requires that it be immediately incorporated into the deoxyglucose by means of a series of automated chemical reactions carried out in a "hot chamber" prepared for this purpose. Next, the marked FDG, since it has a half-life of only 109.8 minutes, is distributed to the corresponding centers in the most efficient way quick possible **(Figure 2)**.

Mechanism of Action and Metabolism

18FDG is undoubtedly the most important PET radiopharmaceutical. This is due not only to its application to the study of very diverse pathologies, but also to its metabolic characteristics and to the speed of its synthesis.

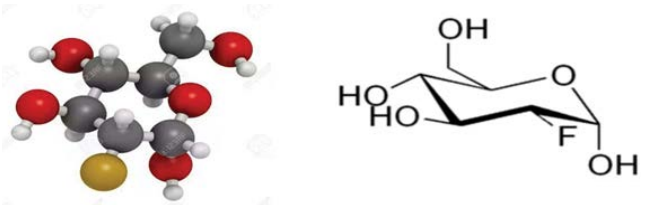

Figure 1 Fluordeoxyglucose.

Figure 2 Cyclotron (particle accelerator) RFCA in the city of knowledge.

FDG, as a glucose analogue, is mainly incorporated by those cells with high rates of glucose consumption such as the brain, kidney and cancer or inflammatory cells, where phosphorylation prevents it from being released into the medium. The metabolically active cells show an increase in the expression of glucose transport proteins, which introduce the FDG inside the cells, where it is phosphorylated to 18F-FDG-6-Phosphate. 18F-FDG-6-Phosphate is trapped in the cytoplasm, since the enzyme Glucose-6-Phosphate-Dehydrogenase has no action on this variant of glucose, stopping at this stage the metabolism of fluorinated glucose. This fact, and the overexposure of the GLUT transport proteins, allows the FGD to accumulate inside the cell and there is a higher concentration of the tracer in the metabolically active cells in relation to the normal tissue, which provides a high contrast ratio. While the radioactivity of the FDG remains, the molecule cannot be degraded or used in any metabolic pathway, because of the radioactive Fluorine in position 2 of the molecule. However, as the radioactivity decays, the fluorine will turn into 18O, which will be able to capture a cation of H^+, and thus become Glucose-6-phosphate, marked with heavy oxygen (oxygen-18) totally innocuous in position 2, which may be metabolized normally by any of the ordinary routes used by glucose.

The detection of FDG metabolism using PET or PET-CT equipment allows obtaining tomographic images and quantifying physiological parameters.

In a PET of the whole body performed between one and two hours after intravenous administration of 18F-FDG, the brain, heart, and urinary tract they are the most prominent sites of radiopharmaceutical accumulation. The brain, an obligate user of glucose, always has priority relative to the rest of the body. Both supratentorial and infratentorial gray matter avidly capture 18F-FDG, and its uptake level is in the typical range of neoplasms

with uptake of 18F-FDG. The myocardium has a similar uptake of 18F-FDG in the postprandial state, but with a sufficiently long fast (typically more than 12 hours), myocardial metabolism changes to the consumption of fatty acids as an energy source, and myocardial uptake is it becomes largely indistinguishable from the activity of the radiopharmaceutical in blood. 18F-FDG has a route of urinary elimination, and in the absence of aggressive hydration, diuretics and urinary catheterization, is present in the bladder and in varying degrees in the upper urinary tract.

In any part of the body, the activity of the radiopharmaceutical is distributed at low levels in recognizable anatomical structures in images corrected for attenuation. The vascular bed of the great mediastinal and cardiac vessels is indistinguishable in comparison with the very low uptake of the lungs. The liver and spleen are associated with slightly higher 18F-FDG activity than the vascular bed, and are reliably identified in the abdomen, as are the kidneys. The pancreas is usually not detected. The intestines are observed in varying degrees, as is the case with the stomach, due to a very broad level of uptake of 18FFDG in the digestive tract. Bone marrow is normally associated with uptake of 18F-FDG at slightly higher levels than blood activity, vertebral bodies are continuously identified, as well as other skeletal structures that contain bone marrow such as the pelvis, hip and sternum. The lymphoid tissue in the neck that is associated with the palatine tonsils is consistently shown to be avid for 18F-FDG and is typically clearly visible. 18F-FDG activity in the neck associated with laryngeal musculature or thyroid tissue is frequently observed. The glandular tissue of the breast is associated with low levels of uptake, slightly higher than that of the mediastinal blood bed in young women.

At rest, skeletal muscle uses an oxidative metabolism of fatty acids to obtain energy. With an increased energy demand, glycolysis becomes the main source of energy for skeletal muscle and depends on the relative delivery of oxygen and the oxidative capacity of the tissue. Rapid muscle fibers, with limited mitosis and limited oxidative capacity, are associated with a high and constant demand for glucose. The extraocularis muscles routinely show elevated 18F-FDG accumulation [1-3].

Molecular Structure

Formula: $C_6H_{11}FO_5$

2-18F-fluoro-2-deoxy-D-glucose (18F-FDG) is a glucose analogue in which the hydroxyl group of carbon has been replaced by a fluorine atom **(Figures 3 and 4)**.

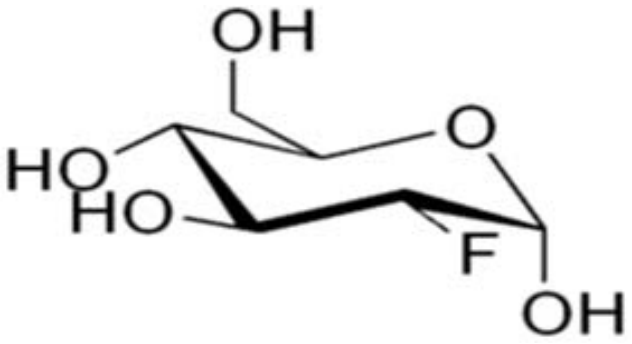

Figure 3 Structure of 2-18F-fluoro-2-deoxy-D-glucose (18F-FDG).

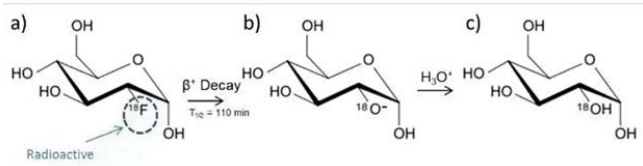

Figure 4 Molecular structures of 2-18F-fluoro-2-deoxy-D-glucose (18F-FDG).

Process

a) Fluorodeoxyglucose b) B decays of a proton emits a positron (and changes of fluorine oxygen); from a positron it is the equivalent antimatter of an electron, when it finds the nearest electron that will annihilate. The question will cease to exist and will be converted into energy in the form of gamma rays of light. The two gamma rays produced each will have 511 keV of energy. c) With a little acid, the product will go to glucose and continue through the cycle of energy in the cell. Until the radioactive decay, the molecule is stuck. There is no chemistry available to the cell to process the glucose with substituted fluorine, once the F is converted to the hydroxyl group, the chemistry can proceed as normal (with a heavy but stable oxygen atom). As a conclusion, we can emphasize that the CT shows the anatomical detail to give the specialist the exact location, size and shape of the diseased tissue or tumor, detected by PET. PET-CT has demonstrated a diagnostic accuracy superior to PET alone, allowing a definitive diagnosis in 20-40% more cases than with PET, and its use has led to changes in the therapeutic management of a high percentage of patients. The fact of combining single exploration anatomical and functional information simultaneously makes this technology present several advantages over PET and CT alone. Because glucose metabolism is a disseminated process, there is normal uptake of 18F-FDG in many locations throughout the body. The tumors generally have a high uptake of 18F-FDG, which allows their detection using PET. Knowledge of the distribution and normal variants of 18F-FDG uptake is essential to differentiate the pathological from the physiological.

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