



Mechanisms Of Localization

OVERVIEW:

To the patient, all radiopharmaceuticals appear to be the same- a clear, colorless liquid. However, we know that different molecules are used to image different organs based on the organ function. For example, it is logical that labeled phosphates would be suitable for imaging bones, as uptake of inorganic phosphate and subsequent incorporation into bone tissue are well documented.

Additionally, insoluble radiopharmaceuticals such as Tc-MAA and Tc-SC are used to image lungs and liver/spleen, respectively, because it is well known that these two organs remove particles from the blood stream based entirely upon particle size. This uptake is totally unrelated to chemical composition. For example, Tc-99m oatmeal with a particle size distribution in the range of 0.1–2 μm would make an excellent liver/spleen agent.



MECHANISMS OF LOCALIZATION

- Capillary Blockade
- Phagocytosis
- Compartmental Localization
- Active Transport
- Chemisorption (also known as Physicochemical Adsorption)
- Cell Sequestration
- Exchange Diffusion
- Simple Diffusion (also known as Passive Diffusion)
- Antigen/Antibody Reaction
- Receptor Binding
- Metabolic Trapping

In order for the mechanisms of localization **to produce excellent quality images**, other factors are important:

- The radioisotope should be a pure gamma emitter, ideally Tc-99m.
- Gamma energy should be between 100-250 keV
- The t_{eff} should ideally be about 1.5 times duration of test
- It is very important to have a high target:non-target ratio

In order for the mechanisms of localization **to produce excellent therapeutic results**, other factors are important:

- The radioisotope should be a pure β^- or α emitter
- Energy should be high (> 1 MeV)
- t_{eff} should be moderately long, e.g., days
- Critical to have a high target:non-target ratio



CAPILLARY BLOCKADE

- Pulmonary perfusion imaging is performed following an IV injection of a radiolabeled, precipitated, biodegradable macroaggregate of human serum albumin
- Radiopharmaceutical: Tc-99m MAA
- Diameter of average capillary: 7-8 μm ; legal particle size range: 90% of all particles must be between 10-90 μm ; 0% >150 μm
- Ideal number of particles to be injected:
 - adult w/o pulmonary HTN: 200K - 700K
 - adult w/ pulmonary HTN: 150 K
 - child (scaled up by body mass) 100K-350K
 - neonate (0-1 yr old) 50 K
- 1/100,000 capillaries blocked by typical injection
- $t_{\text{biol}} = 5-12$ hr depending upon manufacturer
- Imaging performed immediately after injection

PHAGOCYTOSIS

- Reticuloendothelial system imaging is performed following the phagocytosis of radiocolloid particles by Kupffer cells in the reticuloendothelial System following IV injection of the radiolabeled colloid
- Radiopharmaceutical: Tc-Sulfur Colloid
- Diameter of average capillary is 7 μm . Particle size range of Tc-SC is 0.1-2.0 μm , so capillary blockade does not occur.
- Distribution in RE System: 80-90% in liver, 5-10% in spleen; 5-10% in marrow.
- t_{biol} of Tc-SC: infinitely long
- $t_{1/2}$ of clearance from the blood pool: 2.5 min
- Imaging performed 10 min post

COMPARTMENTAL LOCALIZATION

Defined as the placement of a radiopharmaceutical in a fluid space, and then imaging that fluid space

EXAMPLES:

PULMONARY VENTILATION IMAGING

- Mechanism: Compartmental localization of the inhaled radioactive gas within airways in the lungs
- Radiopharmaceutical: Xe-133 gas- contains no particles
- Immediate distribution to lungs; since Xe gas is lipophilic and can cross cell membranes, it dissolves in pulmonary capillaries and is circulated through blood stream, permitting cerebral blood flow studies.
- t_{biol} of Xe-133 gas in lungs is <0.5 min in most patients.

BLOOD POOL IMAGING

- Mechanism: Compartmental localization of autologous radiolabeled red cells within the blood pool
- Radiopharmaceutical: Tc-99m RBC's
- Particle size: approximately 7 μm for Tc-RBC's
- Immediate distribution within blood pool; ultimately Tc-99m dissociates from injected compounds and is cleared through the kidneys.
- t_{biol} of Tc-99m RBC's, 15-25 hr

CISTERNOGRAM

- Mechanism: Compartmental localization of material injected directly into CSF via lumbar puncture.
- Radiopharmaceutical: In-111 DTPA; t_{biol} of In-DTPA is approximately 20 hr.
- Particle size: none- compound is soluble.
- Immediate distribution within CSF; ultimately bathes brain and brain stem; indicates presence of CSF leakage in nasopharynx; eventually cleared through the kidneys.

VOIDING CYSTOGRAM

- Mechanism: Compartmental localization of liquid infused into urinary bladder.
- Radiopharmaceutical: Tc-99m SC
- Particle size: 0.1-2.0 μm
- Immediate localization in bladder; rapidly emptied via catheter into container for counting of radioactivity.
- t_{biol} is measured in minutes.



ACTIVE TRANSPORT

Defined as utilization of a normally active, energy-dependent metabolic pathway in the body to move a radiopharmaceutical across a cell membrane and into the cell.

EXAMPLES:

THYROID UPTAKE/SCAN

- Mechanism: Active Transport. Iodide is trapped, undergoes intermediate syntheses involving a thyroglobulin intermediate, and is ultimately organified into T_3 & T_4 .
- Radiopharmaceutical: I-123 sodium iodide or I-131 sodium iodide.
- Particle size: none- compound is soluble
- Initial localization in thyroid, stomach, and parotids; ultimately stored in thyroid or cleared through the kidneys
- t_{biol} in thyroid: 24 days.

MYOCARDIAL PERFUSION

- Mechanism: Active Transport of radiothallium. This involves utilization of the normally operative energy dependent metabolic pathway for handling potassium since thallos ion (Tl^{1+}) and Rb ion (Rb^{1+}) are potassium analogs and are therefore included in the well documented ATPase-driven Na/K pump mechanism.
- Radiopharmaceutical: Tl-201 chloride, Rb-82 chloride.
- Particle size: none. Compound is soluble
- Initial localization in heart, liver, muscle; ultimately recycled so very little is cleared through the kidneys
- t_{biol} in whole body: 10 days.

RENAL IMAGING

- Mechanism: active transport if compound is processed by tubular secretion.
- Radiopharmaceutical: Tc-MAG3 for tubular secretion studies. Particle size: none- compounds are soluble
- Approximately 80+% of MAG3 by tubular secretion, the remainder by GFR.
- Imaging begun immediately post injection and acquisition is divided into 3 min frames, permitting generation of renogram curves.



CHEMISORPTION (aka Physicochemical Adsorption)

EXAMPLES:

SKELETAL IMAGING

- Mechanism: The phosphate or phosphonate groups on currently used bone agents bind instantaneously, avidly, and essentially irreversibly to the hydroxyapatite structure of bone tissue. In addition, by the same mechanism, they localize in lesions metastatic to bone. Hydroxyapatite is simply tricalcium phosphate
- Radiopharmaceutical: Tc-99m MDP or Tc-99m HDP or Tc-99m PYP.
- Particle size: none- compounds are soluble
- In adults, ~45-50% of the injected dose localizes in bone; the remainder is excreted through the kidneys, probably by GFR. Imaging typically begun 3 hr post injection. In children, skeletal uptake is usually 75-80% of the injected dose.

IMAGING OF ACUTE MYOCARDIAL INFARCTIONS

- Mechanism: chemisorption. When myocardial cells become necrotic following an acute myocardial infarction, there is an influx of calcium ions which are chemically converted to hydroxyapatite crystals. Tc-99m pyrophosphate binds avidly and irreversibly to these crystals at the periphery of the infarct where some perfusion is maintained (none localizes in the central region of the infarct).
- Radiopharmaceutical: Tc-99m Pyrophosphate.
- Particle size: none- compound is soluble.
- Images taken approximately 2 hr post injection. Optimal imaging time post-infarct is 1-3 days; after 6 days an infarct is considered "old" and rate of false negative studies increases significantly.

IMAGING OF ACTIVE THROMBOSIS

- Mechanism: chemisorption. In the presence of active thrombosis, Tc-Acutect (currently unavailable) deposited on the thrombus surface. This permitted external detection of the thrombus using either counting or imaging techniques.
- Radiopharmaceutical: Tc-Acutect
- Particle size: no particles present
- Minimal liver and spleen uptake
- Imaging at 2-4 hr- rapid diagnosis



CELL SEQUESTRATION

EXAMPLE:

SPLEEN IMAGING

Spleen only imaging involves radiolabeling and then heat damaging of patient's red cells to take advantage of the spleen's normal function, i.e., removal of damaged red cells. This procedure permits visualization of the spleen with minimal visualization of the liver. Rarely performed, but considered a classical mechanism of localization of radiopharmaceuticals.

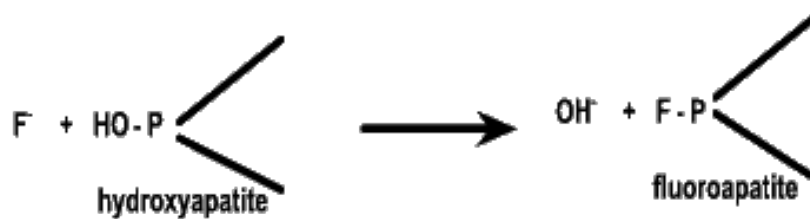
Radiopharmaceutical: Tc-99m damaged autologous red cells.

Particle size: $\sim 7 \mu\text{m}$

Long t_{biol} ; probably in the range of 10-20 hr

EXCHANGE DIFFUSION

By the process called exchange diffusion, radiofluoride ion diffuses into bone tissue and exchanges with hydroxide ion, an integral part of the hydroxyapatite structure, to form fluoroapatite. Binding is essentially irreversible.



SIMPLE DIFFUSION (aka Passive Diffusion)

Following inhalation of Xe-gas, some of the Xe undergoes passive diffusion through membranes in the lungs due to its lipophilic nature and is transported via the blood stream to other parts of the body. This resulting blood concentration permits performance of a cerebral blood flow study.

ANTIGEN/ANTIBODY REACTION

- Tumor imaging and therapy with labeled monoclonal antibodies may be performed following injection of radiolabeled antibodies specific to tumor antigens
- Forms an insoluble antigen-antibody complex that is precipitated at tumor site.
- Radiopharmaceuticals: In-111 Proscint for imaging prostate carcinoma, Y-90 Zevalin for Radioimmunotherapy of non-Hodgkin's lymphoma
- Some liver uptake always observed; small percent localizes in tumor; excretion is typically through kidneys or GI tract
- Imaging typically begun several hours post injection; may continue out to 5 days with In-111 or I-131 compounds



RECEPTOR BINDING

- Imaging tumors with somatostatin receptor sites may be accomplished following an IV injection of a radiolabeled polypeptide chemically analogous to somatostatin. This compound (Octreotide or Octreoscan) binds to somatostatin receptor sites in a wide variety of tumors.
- Radiopharmaceutical: In-111 Octreoscan
- Intense kidney uptake; small percent uptake in tumor; excretion through kidneys

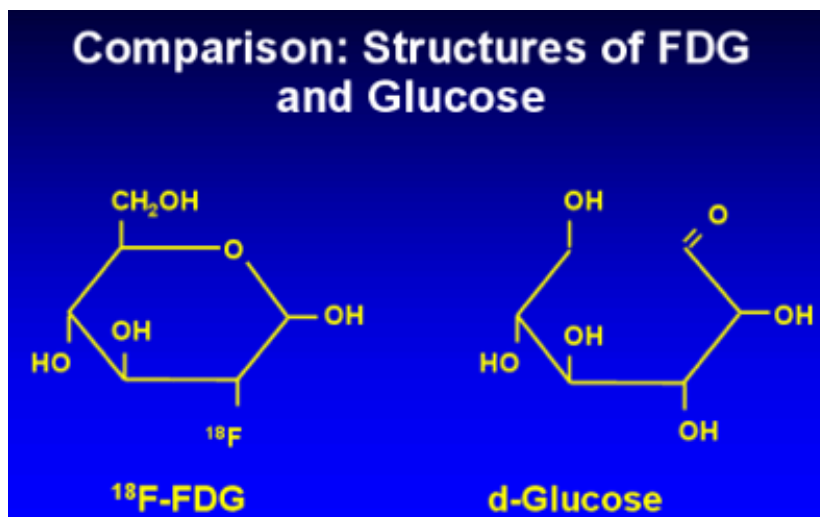


METABOLIC TRAPPING: IMAGING OF MALIGNANT TUMORS

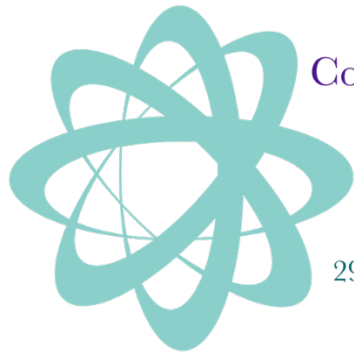
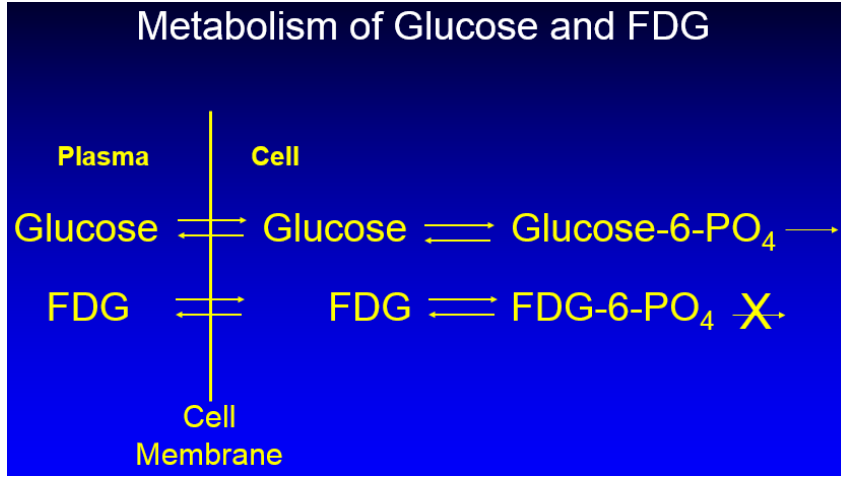
This mechanism involves IV injection of a radiolabeled sugar analog (but not a sugar!) This analog may be trapped by cells for cell metabolism. Tumors, with their higher-than-normal metabolic rate, are able to take up and retain more molecules per gram than normal tissue, resulting in an accumulation of the radioisotope in the tumor.

- Radiopharmaceutical: F-18 FDG
- Particle size: none- compound is soluble
- Some liver uptake; small percent uptake in tumor, but uptake documented in almost every type of tumor
- Imaging typically begun 60-90 min post injection; imaging possible only for several hours post injection due to short half-life of F-18 (110 min)

Comparison: Structures of FDG and Glucose



Metabolism of glucose and FDG



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