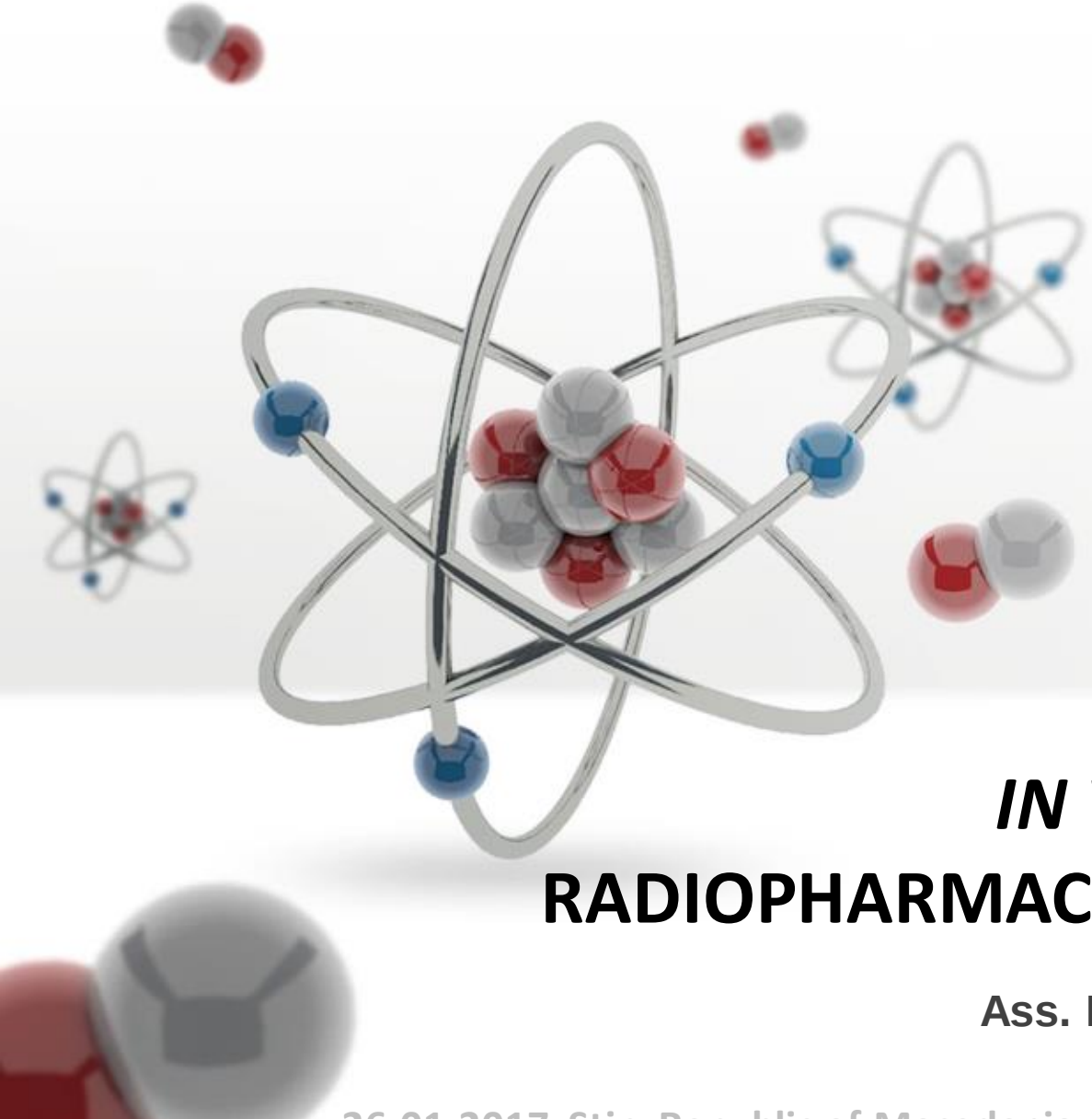
УНИВЕРЗИТЕТ
„ГОЦЕ ДЕЛЧЕВ“
ШТИП

IAEA
International Atomic Energy Agency



IN VIVO KINETICS OF RADIOPHARMACEUTICALS - ADME

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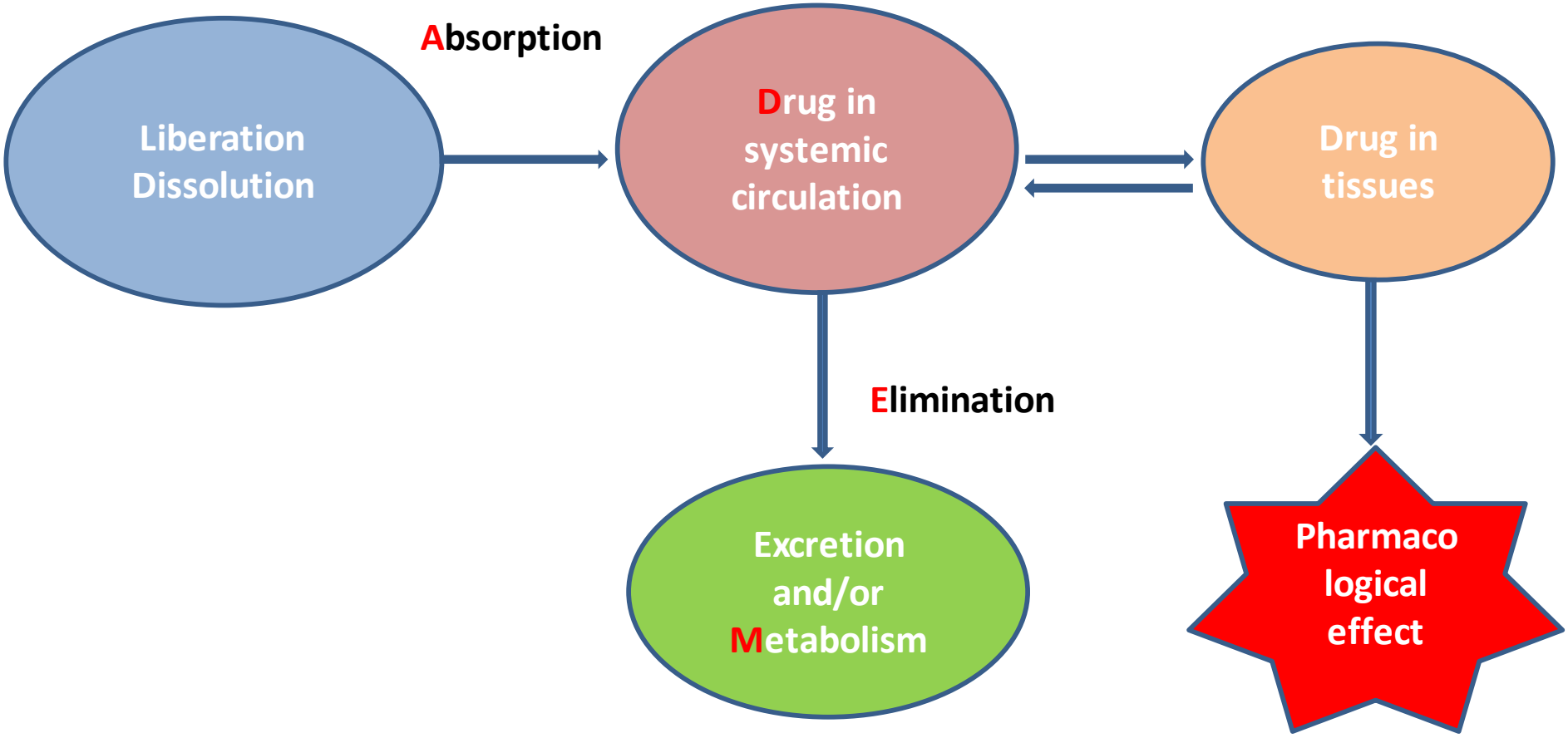
ADME


Liberation
Dissolution
Absorption
Drug in
systemic
circulation
Drug in
tissues
Elimination
Excretion
and/or
Metabolism
Pharmaco
logical
effect

Factors influencing ADME

A. Physico-chemical properties of the element (radioactive isotope)

B. Physico-chemical properties of the radiolabeled drug

C. Organ/tissue characteristics

A

Common elements used in NM their dominant localization and excretion

Element	Dominant localization	Dominant excretion
Rb	Muscule	Urine
Cs	Muscule	Urine
Cu	Liver	Urine
Ag	Protein	Feces
Au	Liver	Urine
Sr	Bone	Feces
Ba	Bone	Urine+Feces
Ra	Bone	Urine+Feces
Ga	Bone, muscle	Feces
In	Bone, liver	Feces
Tl	Muscle	Feces

A

Common elements used in NM their dominant localization and excretion

Element	Dominant localization	Dominant excretion
Sc	Bone, liver	Feces
Y	Bone	Urine
Sm	Liver, bone	Feces + Urine
Zr	Bone	Feces
P	Muscle, bone	Urine
Cr	Bone, blood	Urine
Mo	Liver	Urine
F	Bone	Urine
I	Thyroid	Urine
Tc	GIT	Urine

B

Physico-chemical properties of the radiolabeled drug

- Ionization/oxidation state /solubility at physiologic pH
- Protein /tissue/cell binding affinity

C

Organ/tissue characteristics

The rate of delivery and potential amount of drug distributed into tissues is determined by

- Cardiac output
- Regional blood flow
- Capillary permeability
- Tissue volume
- Presence of characteristic receptors for the radiopharmaceutical administered

Distribution to well perfused organs is faster (liver, kidney, brain)

Distribution to poorly perfused organs is slower (muscle, most visceral organs, skin, and fat)

Compartmental distribution

One-compartment open model - the simplest way to describe the process of drug distribution and elimination in the body.

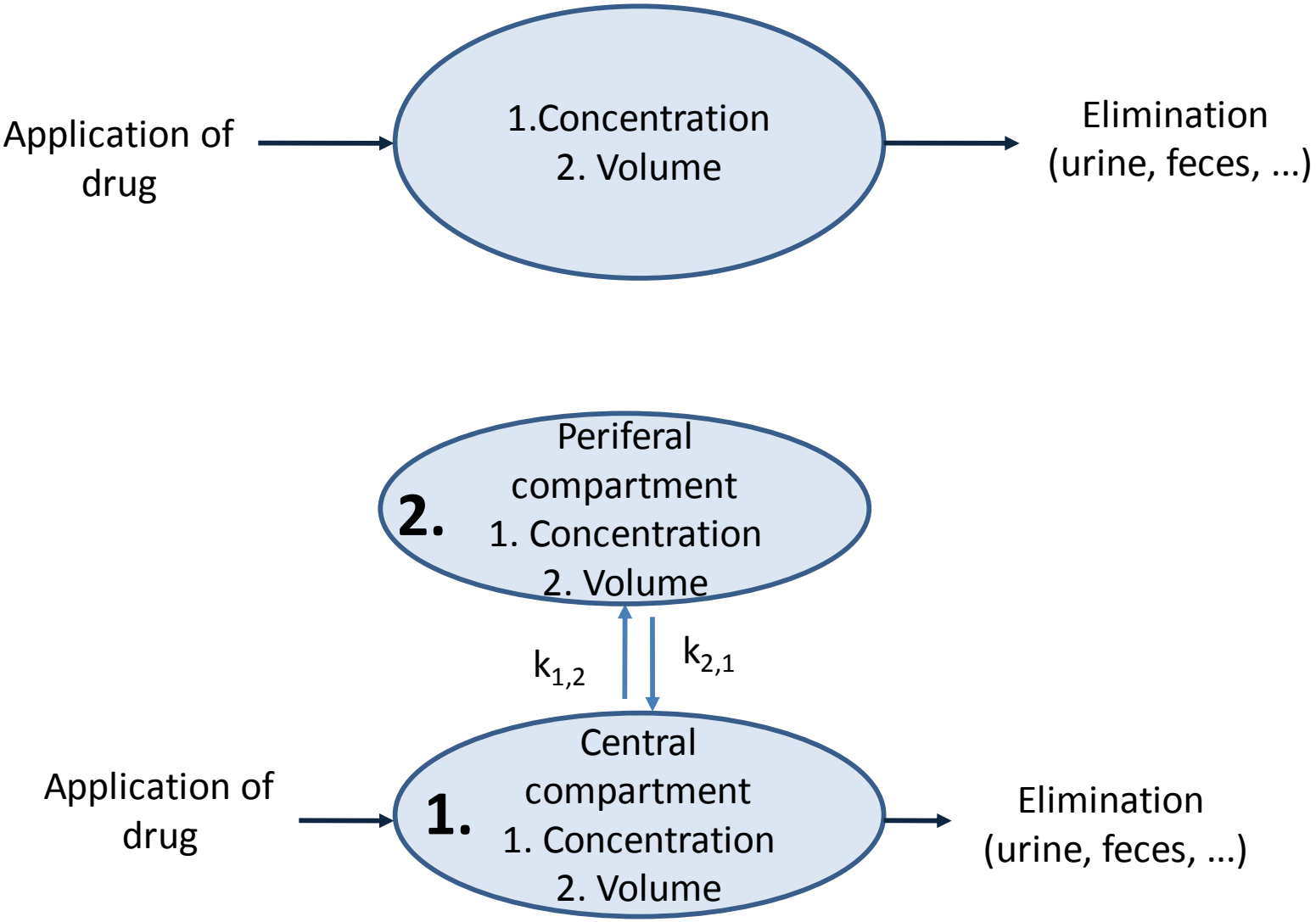
This model assumes:

- the drug can enter or leave the body and the body acts like a **single**, **uniform** compartment.
- the drug is injected all at once into a box, or compartment
- the drug distributes instantaneously and homogenously throughout the compartment.

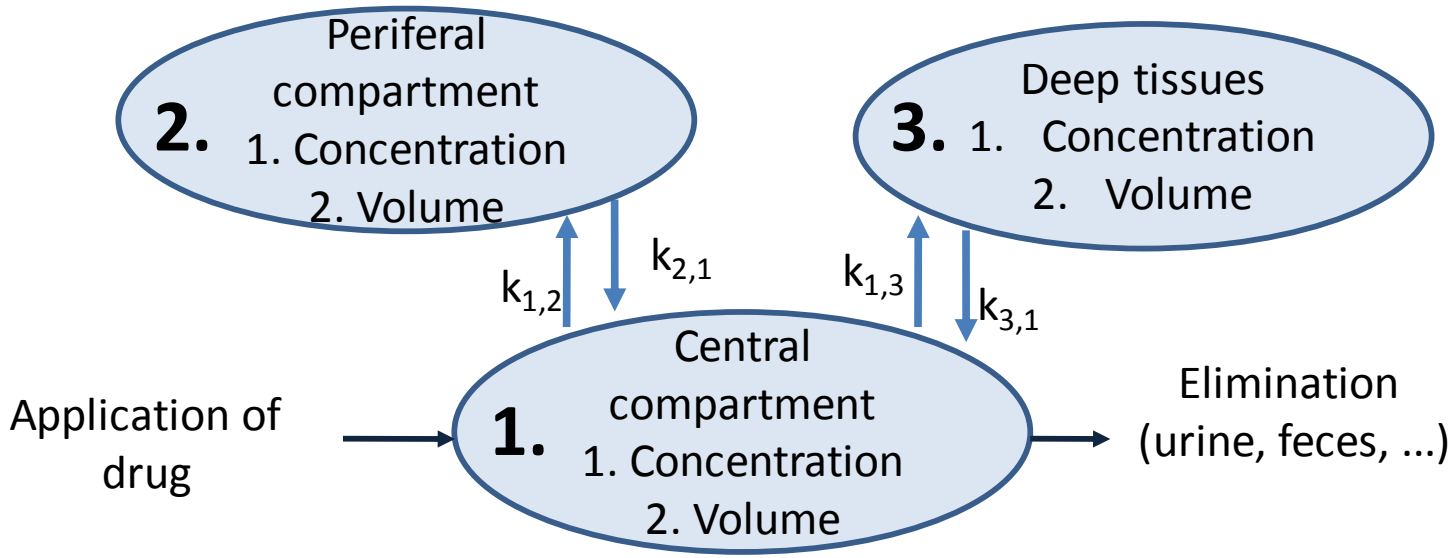
The simplest route of drug administration from a modeling perspective is a **rapid intravenous injection (IV bolus)**.

Drug elimination also occurs from the compartment immediately after injection.

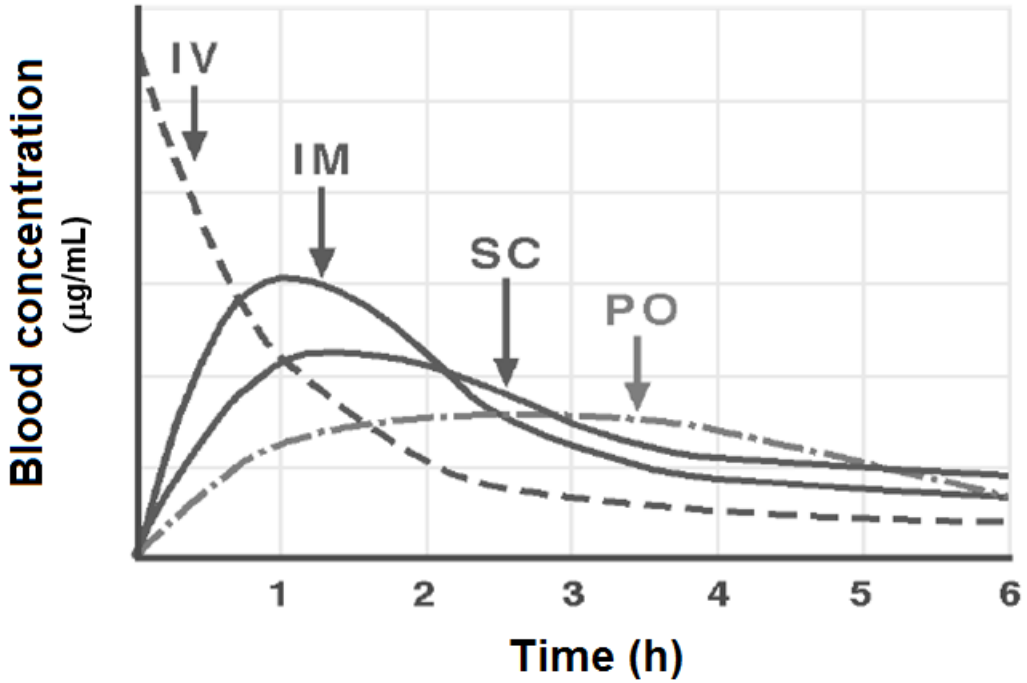
Compartmental distribution



Compartmental distribution



Concentration of drug in blood after various types of administration



Volume of distribution

- The space in which this volume is enclosed is the compartment
- parameter that characterizes the distribution of a drug is the ***volume of distribution (Vd)***
- the ratio of the **dose administered, divided by the plasma concentration**

$$Vd = D/C_0$$

Not an actual volume : very lipophilic drugs have *Vd values that are many times greater than the actual body volume*

In RP, Vd depends on the **route of administration:** lungs volume for aerosol, cerebrospinal fluid volume for the tracer administered intrathecally, blood volume for *i.v. radiopharmaceuticals.*

http://www.icp.org.nz/icp_t3.html

Biodistribution of RPs

Physico-chemical properties of the radiolabeled drug

- **Mw and shape (especially for protein RP)**
- **Protein binding**
- **Lipid solubility/partition coefficient**
- **Presence of specific drug receptors**
- **Specific transport mechanisms**

- **Stability of the radiolabeled compound**
- **Purity of the radiopharmaceutical preparation**
- **Pathophysiological state of the patient**
- **Presence/ absence of interfering drugs**

Protein binding of radiopharmaceuticals

Is greatly influenced by a number of factors, such as:

- **the charge on the radiopharmaceutical molecule**
- **pH**
- **the nature of the protein**
- **the concentration of anions in the plasma**

- Nonspecific binding to albumin and other plasma proteins is correlated positively and linearly with increasing lipophilicity.

- Proteins contain hydroxyl, carboxyl, and amino groups which determine their configuration and the extent and strength of protein binding to the radiopharmaceutical.

- Metal complexes can exchange the metal ions with proteins because of the stronger affinity of the metal for the protein. This process is called **"trans-chelation" and leads to *in vivo metabolism of the complex.***

e.g. ^{67}Ga-citrate exchanges ^{67}Ga with transferrin to form ^{67}Ga-transferrin in the plasma

Protein binding of radiopharmaceuticals

The extent of protein binding of any new radiopharmaceutical should be determined before its clinical use.

Protein-binding of radiopharmaceuticals in plasma samples can be measured by several techniques including:

Size-exclusion chromatography (SEC)

Trichloroacetic acid (TCA) precipitation

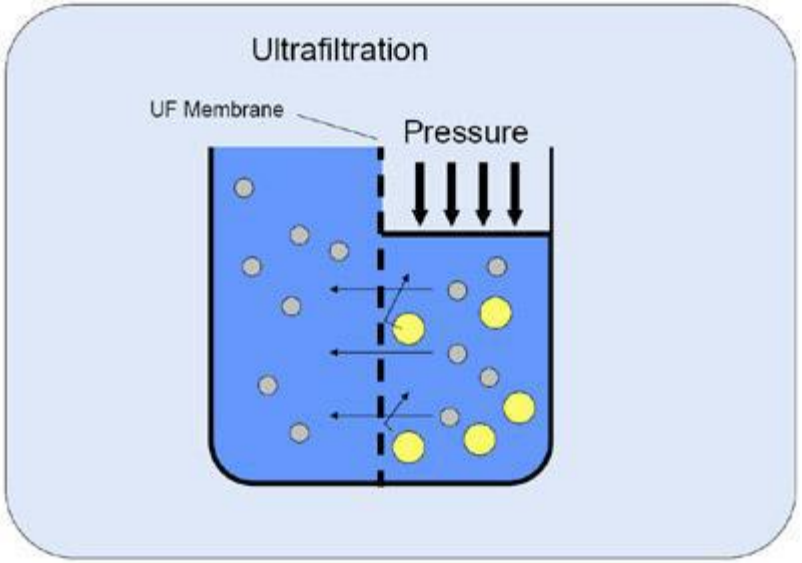
Dialysis

Ultrafiltration

$$\%\text{unbound} = \frac{C_u}{C_t} \times 100$$

Cu - drug concentration in ultrafiltrate(unbound) and

Ct - total drug concentration before the experiment



Protein binding of radiopharmaceuticals

The protein binding of radiopharmaceuticals ranges from negligible (**< 5 %) for ^{201}Tl-thallous chloride and ^{99m}Tc-DTPA (most formulations) to as high as 79-90 % for ^{99m}Tc-MAG$_3$.**

α1-antitrypsin is responsible for binding

^{99m}Tc-exametazime

^{99m}Tc-glucoheptonate

^{99m}Tc-DTPA

^{99m}Tc-iminodiacetic acid agents

Albumin is the main plasma protein involved in binding

^{99m}Tc-medronate (^{99}mTc-MDP) and

^{99m}Tc-DMSA

α2-globulin binds ^{99m}Tc-MAG$_3$

Mechanisms of Localization of RP

Isotope dillution
Capillary blockade
Cellular migration
Cell sequestration
Simple (passive) diffusion
Facilitated diffusion
Active Transport
Phagocytosis
Cascular permeability and capillary leakage
Cell proliferation
Metabolic trapping
Metabolic substrates
Tissue hypoxia
Specific receptor binding / binding to tumor antigens

Isotope Dilution

Diluting a radiotracer (or tracer) of known activity (or mass) in an unknown volume.

Measuring the degree to which the radiotracer was diluted by the unknown volume, one can *determine the total volume (or mass)* of the unknown volume.

- for quantitative determination of RBC volume (mass), plasma volume, and total blood volume the radiotracer *must remain only in the blood volume* to be measured.

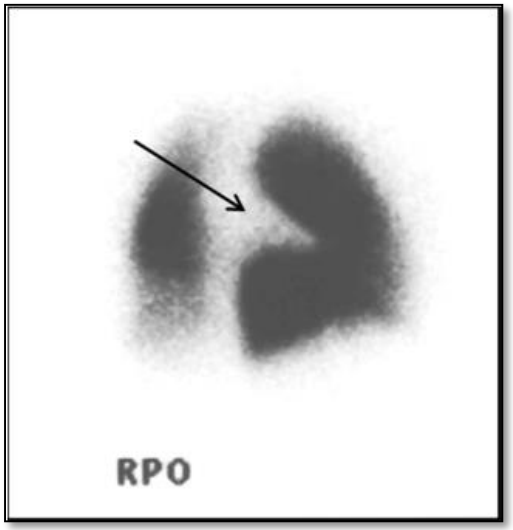
e.g. Nondiffusible, radiolabeled, ^{51}Cr-RBCs are used to measure RBC mass, while ^{125}I-HSA is used to measure plasma volume.

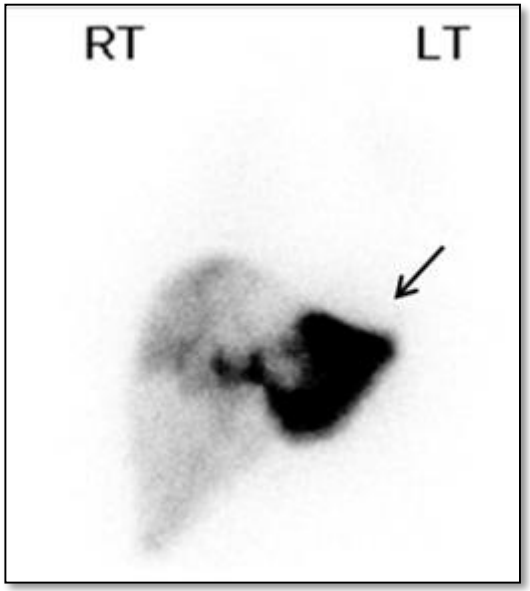
Capillary blockage

Physical trapping of particles in capillaries and pre-capillary arterioles.

- most commonly *used to determine the perfusion to an organ*: lung, heart, or brain.
- ^{99m}Tc-MAA particles generally are in the range of 10–50 µm in diameter.

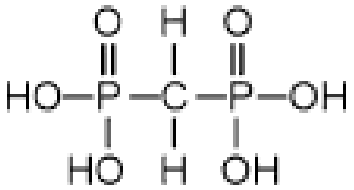
Tc-99m macroaggregated albumin (MAA) for perfusion lung imaging (A) or a similar procedure for evaluation of liver blood flow (B)



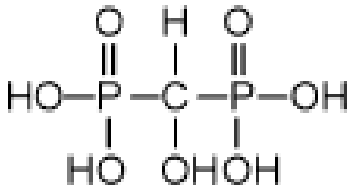


Physicochemical adsorption

- ^{99m}Tc-phosphonates accumulate in hydroxyapatite crystal (containing Ca^{2+} and phosphate ions) matrix or in the amorphous (noncrystalline) calcium phosphate

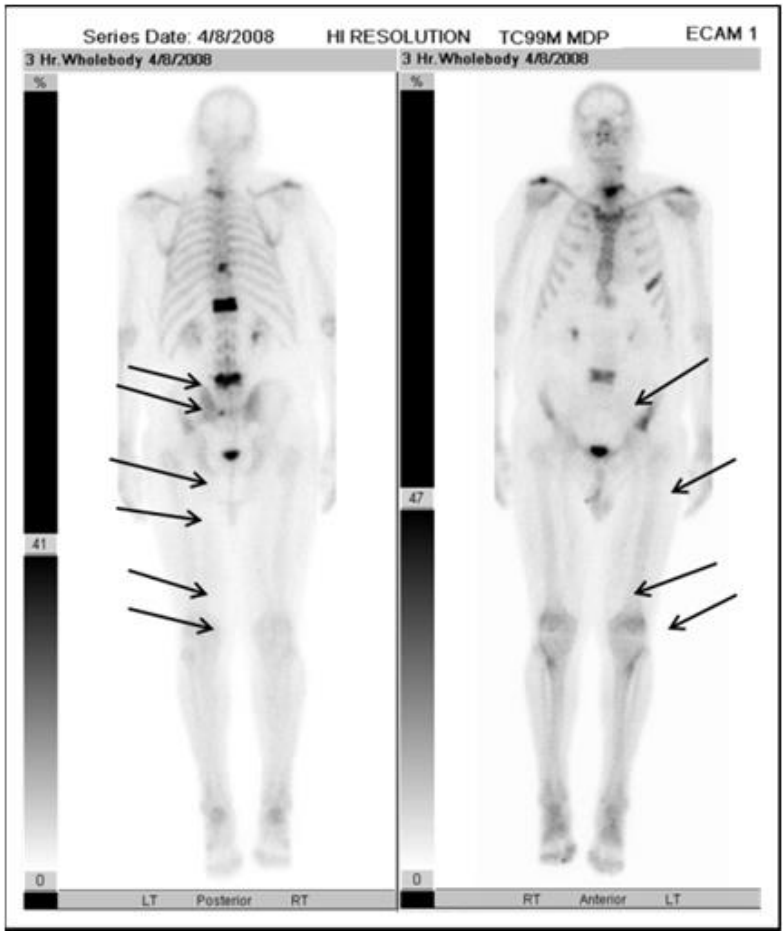


Methylene diphosphonate (MDP)



Hydroxymethylene diphosphonate (HDP)

- Sm-153 lexidronam (EDTMP) for treatment of painful bone metastases.



Tc-99m MDP bone scan shows increased uptake in reactive bone around metastatic tumors

Ion exchange

Exchange of ionic chemical analogs, especially in a crystalline matrix.

✓exhange of Sr^{2+} / Ca^{2+} and F^- / OH^- in hydroxyapatite.

- Bone imaging and bone metastases palliation beta–emmiter $^{89}SrCl_2$ beta-emitter used to treat painful bone metastases,
- $Na^{18}F$, a PET agent used for bone scans

Passive diffusion

- Random movement of molecules with the net effect toward achieving uniform concentration.

✓ passage across a membrane

✓ lipid solubility is an important property

✓ pH/ionization - depending on the pH of the immediate environment

✓ molecular size - small pores, or holes, that allow certain small molecules to pass through. Generally limited to molecules having a molecular weight of *less than 80 daltons*.

Passive diffusion

Fick's law of diffusion

- ✓ the rate of diffusion is a function of the concentration gradient
- ✓ does not require the input of other external energy
- ✓ no transporters, carriers, or other receptors are involved so passive diffusion is *non-selective*
- ✓ not competitively inhibited by similar molecules
- ✓ not subject to saturation

e.g. Gases used for ventilation studies, such as ^{133}Xe, ^{127}Xe, and ^{81m}Kr, are inert lipophlic gases. After their administration through inhalation, these gases are distributed within the lung air spaces by diffusion.

Passive diffusion

Influence of pH/ionization

The extent of ionization of a weak electrolyte depends on

- pK_a of the drug
- pH of the medium

Henderson - Hasselbalch equation

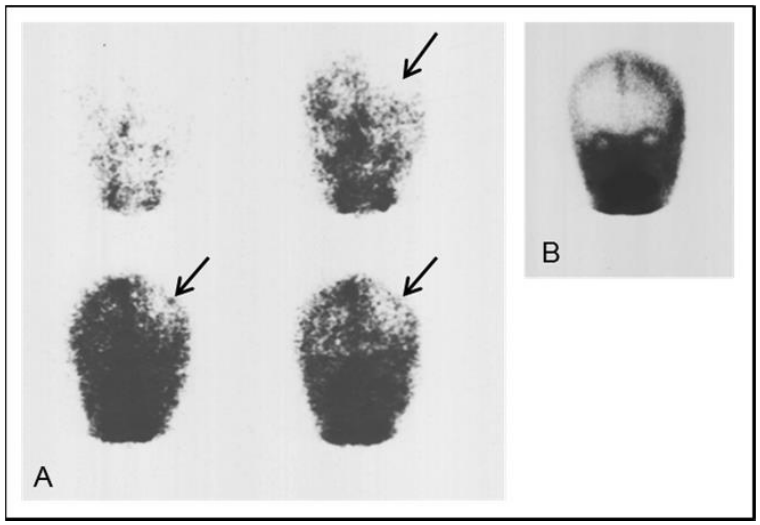
weak acids

$$\text{Ratio} = \frac{[\text{salt}]}{[\text{acid}]} = \frac{[A^-]}{[HA]} = 10^{(pH-pK_a)}$$

weak bases

$$\text{Ratio} = \frac{[\text{base}]}{[\text{salt}]} = \frac{[RNH_2]}{[RNH_3^+]} = 10^{(pH-pK_a)}$$

Tc-99m DTPA brain imaging. Tc-99m DTPA cannot normally penetrate BBB Disruption of the BBB (tumor, stroke, infection) causes Tc-99m DTPA to diffuse across the disrupted BBB and accumulate in that affected area of the brain

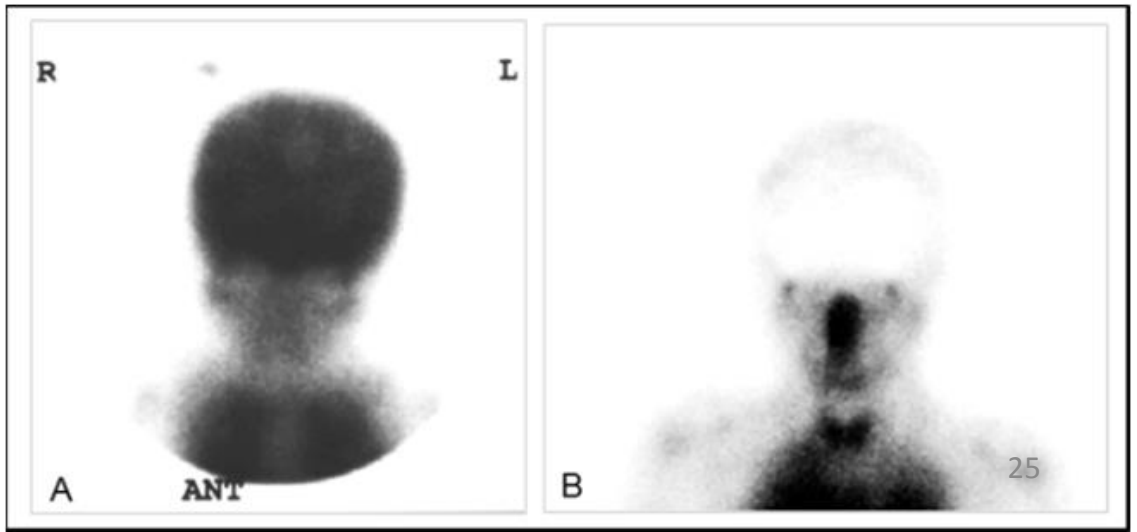


Dynamic imaging after IV injection of Tc-99m DTPA revealing stroke (A)

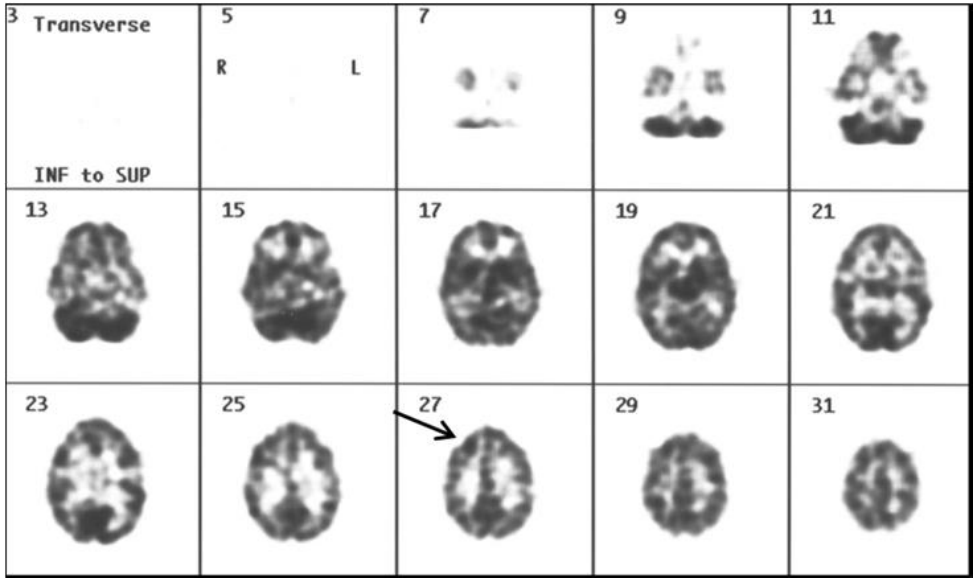
Delayed imaging at 3 hours after Injection (B) shows increased accumulation of Tc-99m DTPA as a result of diffusion across a disrupted BBB.

- ***Delivery via passive diffusion + retention – conversion to hydrophilic species***

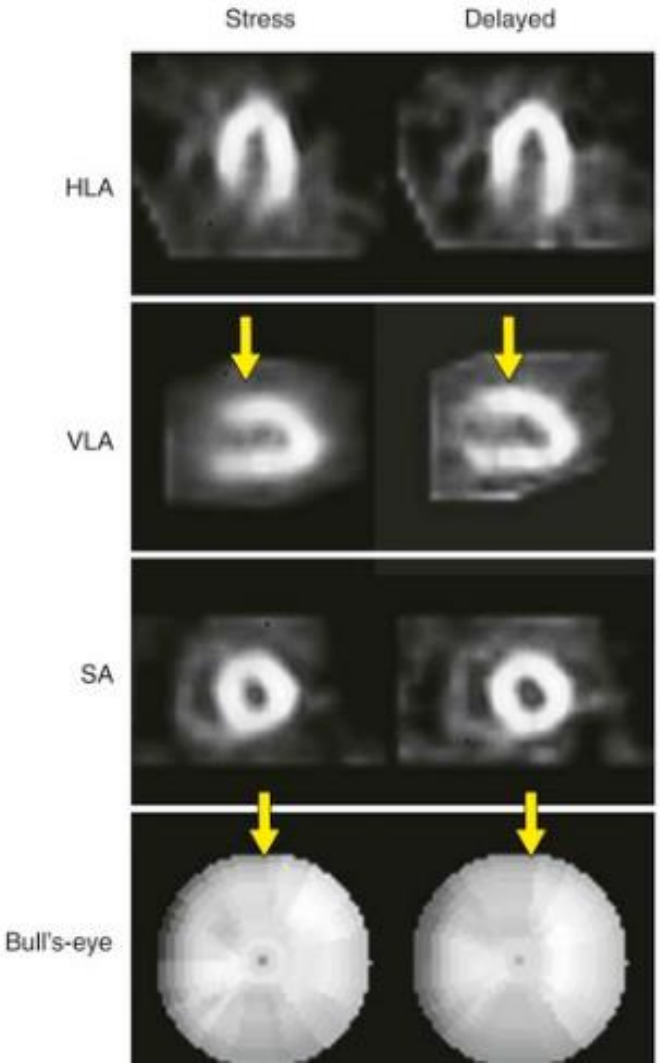
Normal uptake of Tc-99m HMPAO in the brain of a living person (A).



- ***Delivery via passive diffusion + retention – enzymatic metabolism***



SPECT imaging following ictus -injection of Tc-99m bicisate (ECD) shows increased uptake in the seizure focus.



- ***Delivery via passive diffusion + retention by electrostatic binding in mitochondria***

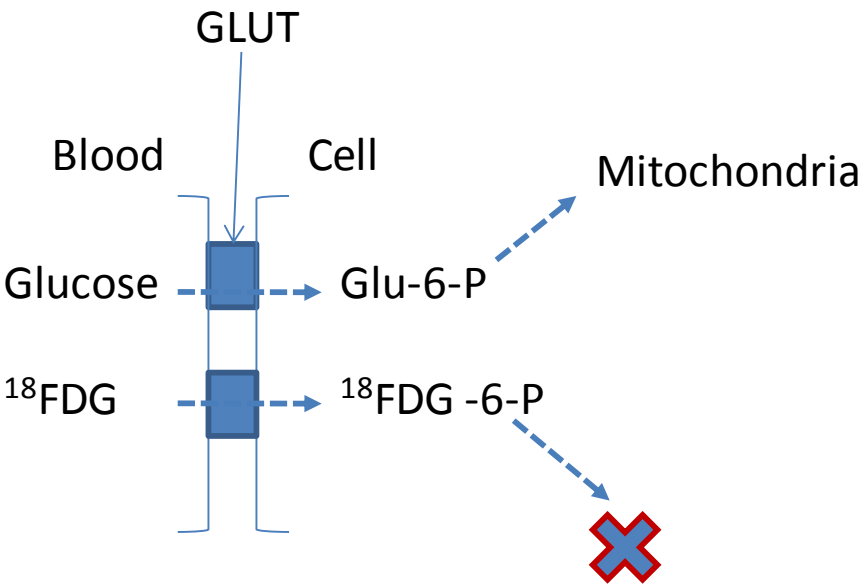
Lipophilic, cationic ^{99m}Tc radiopharmaceuticals (sestamibi, tetrofosmin, and furifosmin) have been developed for imaging myocardial perfusion

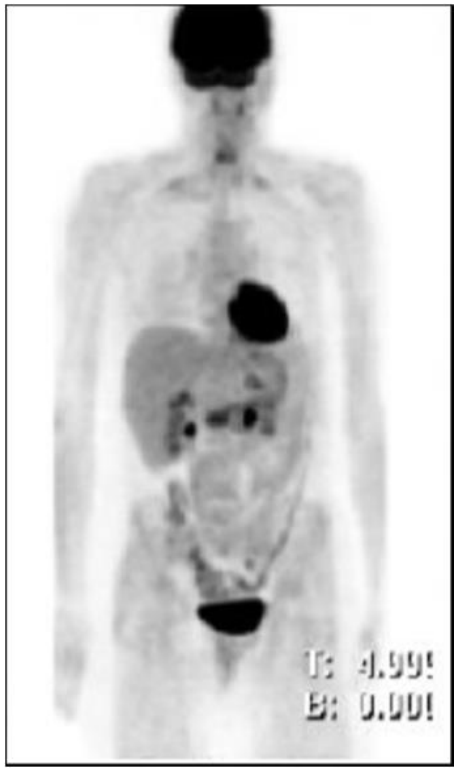
http://clinicalgate.com/nuclear-medicine-imaging-of-myocardial-perfusion/

Facilitated diffusion

- ✓ carrier-mediated, selective
- ✓ can be competitively inhibited
- ✓ limited number of carriers - possible saturation
- ✓ concentration gradient needed
- ✓ does not use external energy

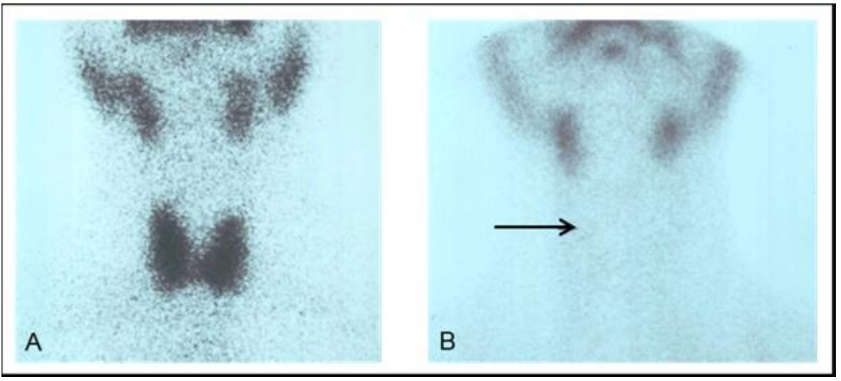
e.g. cellular uptake of ^{18}FDG reflects glucose metabolism



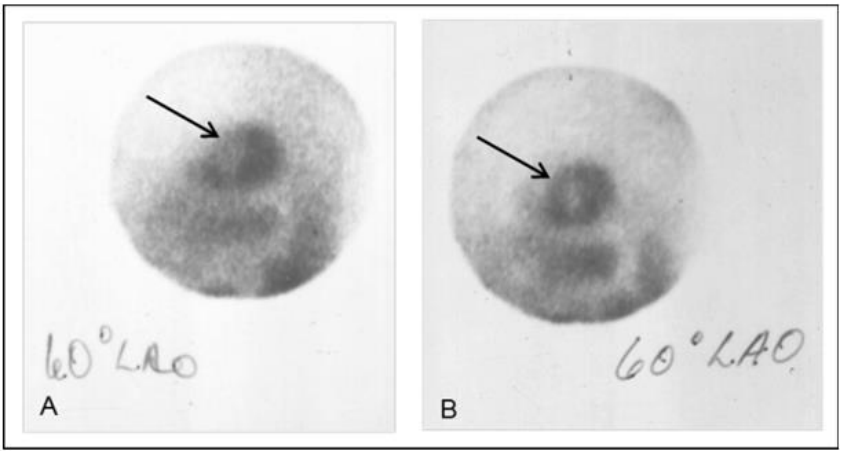


Following injection of ^{18}FDG in a normal patient, there is high brain uptake, variable uptake in heart and moderate uptake in liver, GI tract, and marrow.
^{18}FDG is not reabsorbed by the distal tubules so it remains in the urine.

Active transport



Absent thyroid uptake of Tc-99m pertechnetate in a patient who was administered iodinated x-ray contrast media a few days before.



Reduced uptake of Tl-201 in an area of heart muscle due to stress-induced ischemia in a patient with coronary artery disease (A) Normalization of uptake (B)

- ✓carrier-mediated
- ✓requires energy (ATP)
- ✓selective, can be competitively inhibited
- ✓possible to achieve saturation

e.g. Iodide ions are transported into thyroid cells via the Na^+/I^- symporter.

I-123 and I-131 for thyroid function evaluation.

Tc-99m pertechnetate (TcO^{4-}) is of similar ionic radius and a negative charge so it is also transported like iodide.

e.g. Na^+/K^+ pump, especially of importance in the heart muscle.

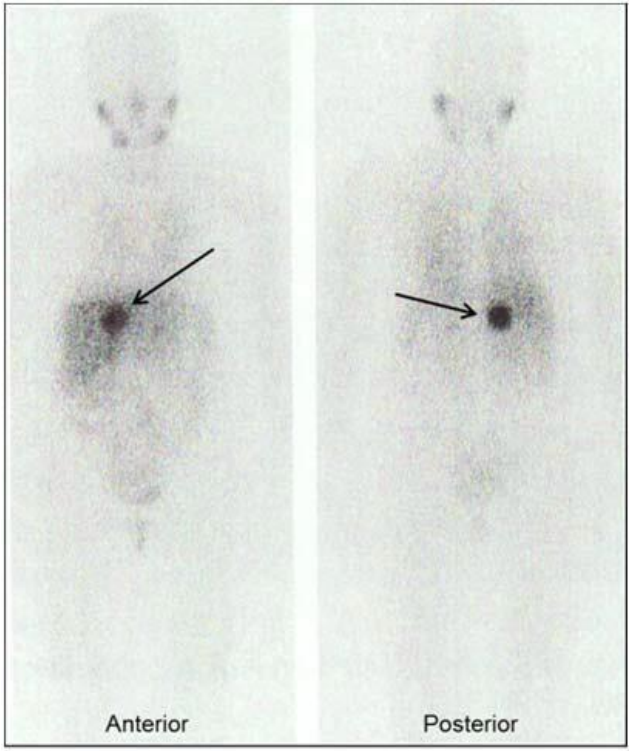
$^{201}TlCl$ myocardial perfusion scans.

$^{82}RbCl$ is used for PET myocardial perfusion scans.

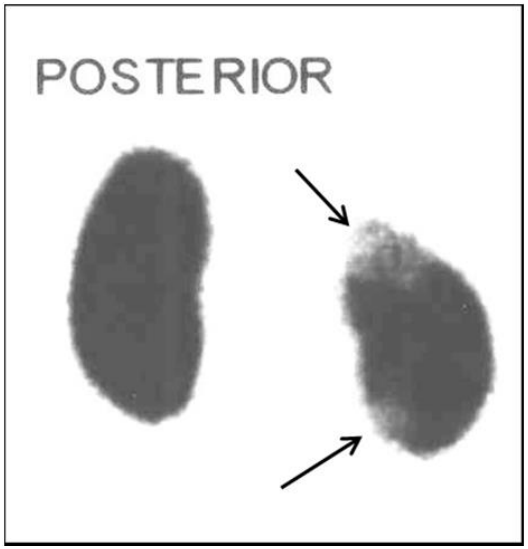
Transport of monoamine neurotransmitters into neurons via norepinephrine transporter

I-123 metaiodobenzylguanidine (MIBG) fits in this transporter.

Overexpression occurs in certain neoplasms such as neuroblastoma and pheochromocytoma



I-123 MIBG demonstrates increased uptake in a pheochromocytoma in the right adrenal gland. Normal uptake is also seen in salivary glands, liver, heart, and bowel.



Active transport in the tubular cells of the renal cortex.

Tc-99m succimer (DMSA) is taken up and retained

Tc-99m DMSA renal scans shows normal uptake throughout the renal cortex. Areas of decreased uptake in both the upper and lower poles of the right kidney are scar formation subsequent to recurrent kidney infections.

Secretion

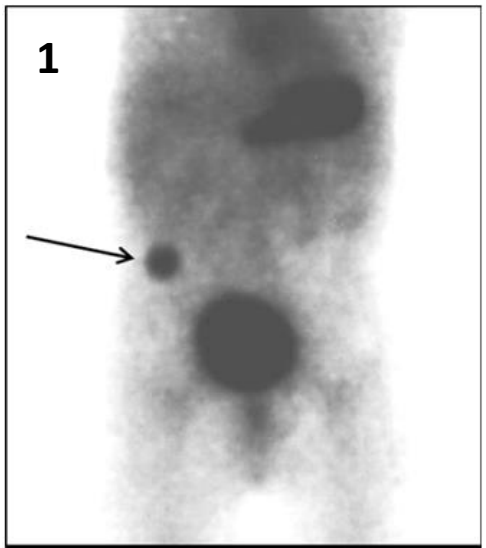
Special case of active transport out of glands and other tissues.

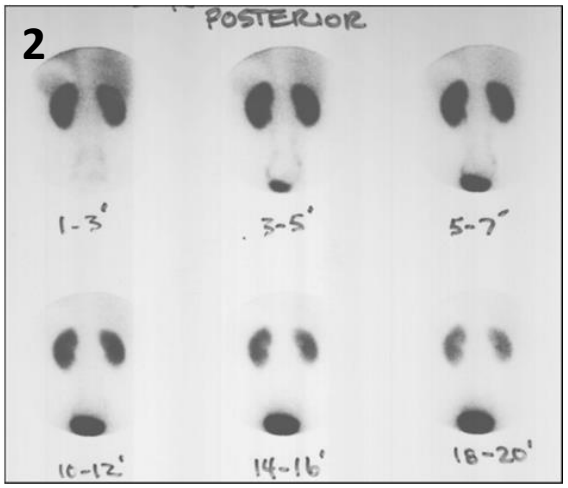
- Gastric secretion, kidney tubular secretion, bile secretion

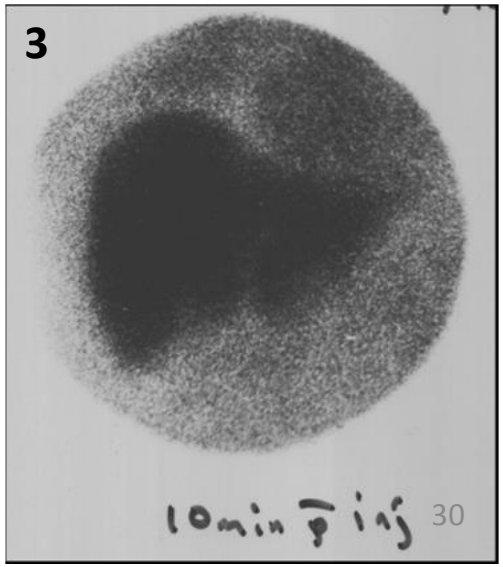
(1) Diagnosis of present Meckel's Diverticulum (a patch of ectopic stomach tissue) using Tc-99m pertechnetate (TcO^{4-}) , ion of similar size and like charge to chloride (Cl^-)

(2) Tc-99m mertiatide (MAG3) for renal scan provides better contrast compared to radiopharmaceuticals eliminated by glomerular filtration

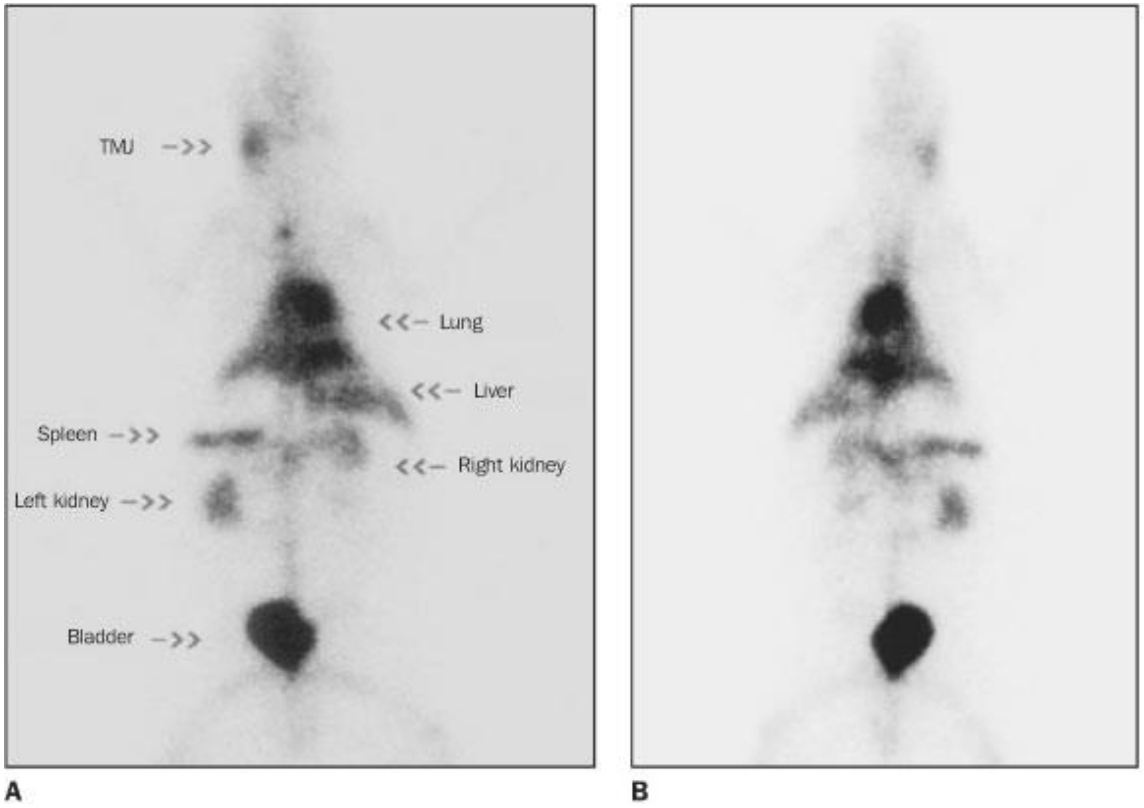
(3) Liver scan with Tc-99m IDA (imino diacetic acid) agents (disofenin, mebrofenin) that are excreted using the same organic ion transport system as is used by bilirubin







Cellular Migration and Sequestration



- ^{111}In-oxine- or ^{99m}Tc-HMPAO-labeled autologous mixed leukocytes (neutrophilic PMNs) are routinely used to image various inflammatory diseases and infectious processes.
- ^{111}In-platelet localization at the site of active thrombus formation

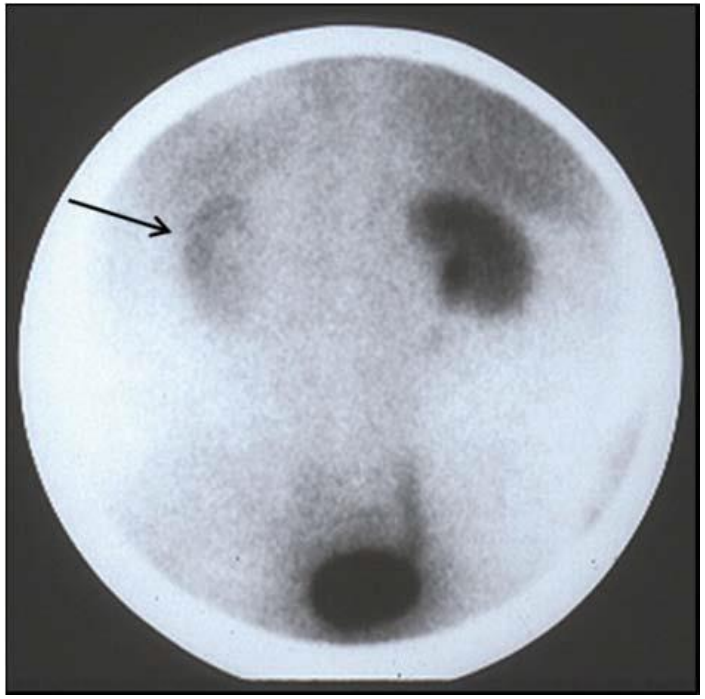
Ventral (A) and dorsal (B) view of physiological distribution of ^{99m}Tc-HMPAO-labeled lleukocytes one hour post injection

Filtration (pore/convective transport)

- ✓ Diffusion involving transit of molecules through pores/channels
- ✓ hydrostatic or osmotic pressure gradient.
- ✓ molecular size vs. pore size. (MW < 5000 in glomerular filtration)

- ✓ requires some sort of force or pressure gradient
- ✓ no transporters, carriers, or other receptors are involved: non-selective, not competitively inhibited by similar molecules, not a subject to saturation

- radiopharmaceutical used for glomerular function renal imaging is Tc-99m DTPA



Pre-treatment with captopril, decreased glomerular filtration of Tc-99m DTPA is seen in the left kidney. As an ACE inhibitor,
captopril blocked the compensatory mechanism activated by left renal artery stenosis, resulting in decreased glomerular pressure in the left kidney

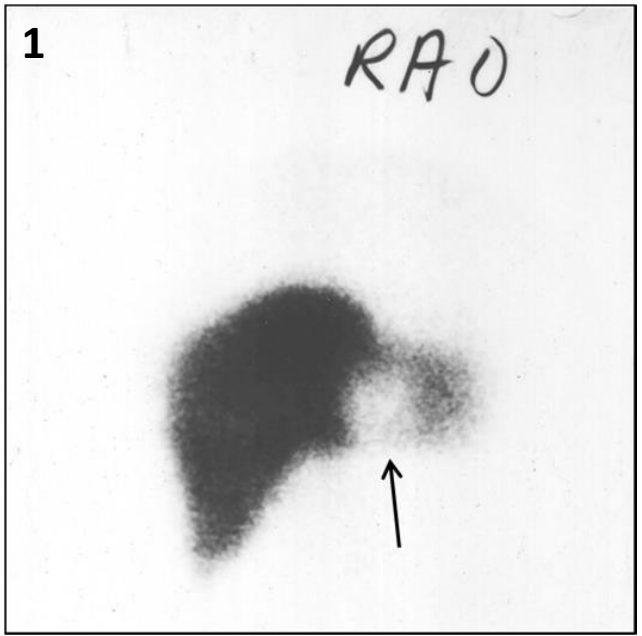
Phagocytosis (vesicular transport)

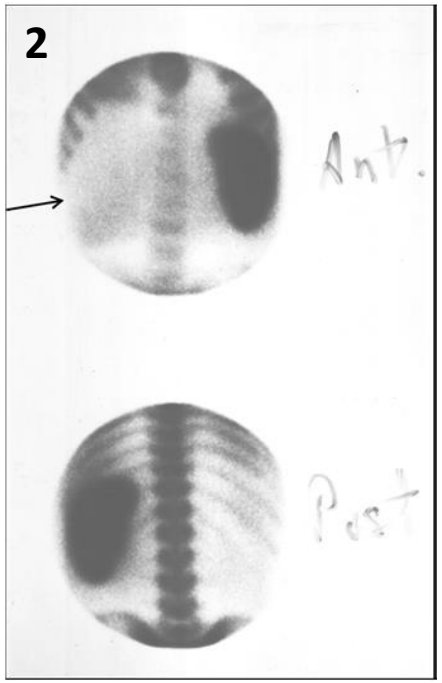
Cells engulf a particle and internalize it.

Reticuloendothelial system (RES) cells (e.g. Kupffer cells in the liver)

- Tc-99m sulfur colloid, the traditional radiopharmaceutical used for liver scans is localized by this mechanism. Focal areas lacking Kupffer cells, such a tumor, cyst, abscess, or hemangioma, will be demonstrated as areas of lack of uptake (1)

In hepatitis or cirrhosis, there is typical 'colloid shift' – i.e., a shift in normal uptake away from the liver with increased uptake in the spleen and bone marrow (2)





Localization of radiolabeled metabolic precursors and substrates

- **Metabolic Trapping of FDG**

- ***Radiolabeled Amino Acids***

L-[methyl-^{11}C] methionine: radiolabeled amino acid uptake within tumors may reflect the increased protein synthesis rate of proliferating tumor cells or simply an increased rate of amino acid transport across the tumor cell membrane

L-[1-^{11}C]tyrosine, L-[2-^{18}F]fluorotyrosine, L-4-[^{18}F]fluoro-m-tyrosine, and L-[3-^{18}F]-a-methyltyrosine (FMT).

Tissue hypoxia imaging

- ^{18}F-fluoromisonidazole (FMISO) the most extensively studied hypoxia-selective radiopharmaceutical

2-nitro in misonidazole (MISO) is transported into the cell by diffusion. In the cytoplasm, the nitro group (NO_2) undergoes enzymatic reduction to the free radical anion. In hypoxic tissue, the free radical is further reduced to a reactive species, hydroxylamine, and then to an amine and attached irreversibly to cellular macromolecules and are retained within the cell.

- ^{64}Cu-ATSM (Cu-diacetyl*bis-(*N4-methylthiosemicarbazone) is selectively trapped in hypoxic tissue but rapidly washed out of normoxic cells and is used for PET imaging

Cell Proliferation

- the growth rate of tumors correlates with their level of differentiation;
- most malignant tumors grow more rapidly than benign tumors→ increased mitotic activity in tumor tissue → increased requirement of substrates (nucleotides) for DNA synthesis
- ^{11}C-Thymidine has been used for many years as a PET tracer to image tumors of the head and neck
- ^{125}I-5-iodo-2'-deoxyuridine (IudR), an analog of thymidine, is phosphorylated and incorporated in DNA
- ^{18}F-Fluoro-3'-deoxy-3'-l-fluorothymidine (FLT)- proliferation tracer (it is phosphorylated by TK, and TK activity is very high throughout the cell cycle in malignant tumors)

Specific Receptor Binding

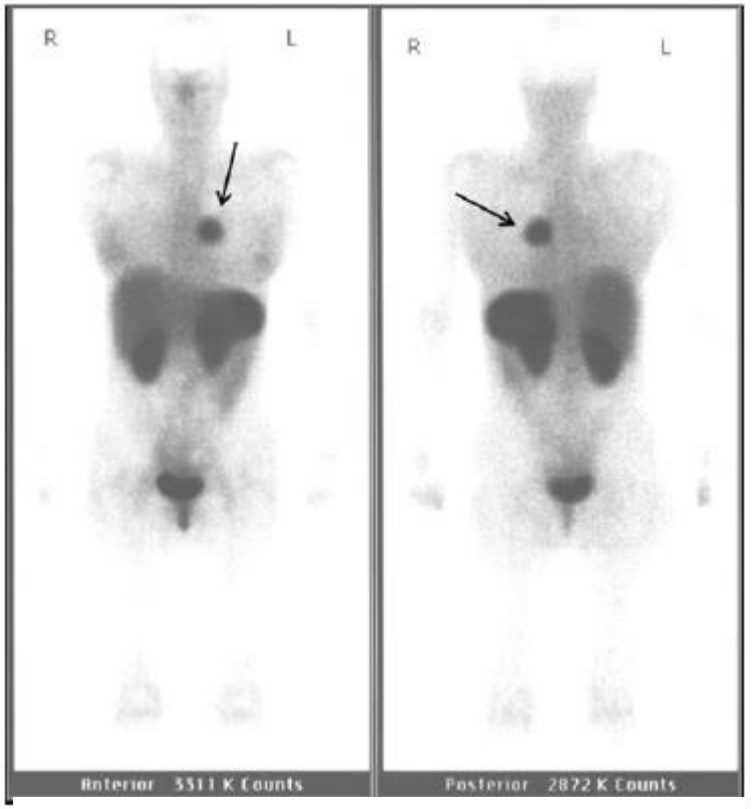
Somatostatin Receptors

Human SST receptors (SSTR) have been identified on many cells of neuroendocrine origin as well as on lymphocytes

- most neuroendocrine tumors, small cell lung cancers, and medullary thyroid carcinomas express SSTRs in high density

Imaging and therapy of SSTR-positive tumors

^{111}In-DTPA-d-Phe1-pentetreotide (Octreoscan), 90Y-DOTA-Tyr3-octreotide (DOTATOC)



In-111 pentetreotide image shows increased uptake in a somatostatin expressing carcinoid tumor in the left lung (arrow). Also seen is normal uptake in liver and spleen, and normal excretion by the kidneys into the urine (bladder).

Specific Receptor Binding

Vasoactive intestinal peptide (VIP) Receptors

- Increased VIP receptor expression has been seen on adenocarcinomas, breast cancers, melanomas, neuroblastomas, and pancreatic carcinomas

- ^{123}I-VIP shows specific uptake in primary tumors as well as in liver, lung, and lymph node metastases of pancreatic adenocarcinoma, colon adenocarcinoma, or gastrointestinal neuroendocrine tumors

Specific Receptor Binding

Steroid Hormone Receptors

Majority of breast cancers are hormone dependent, as indicated by increased expression of intracellular estrogen or progesterone receptors

- 16α [-[^{18}F]fluoro-17 β -estradiol (FES)
- 21-[^{18}F]fluoro-16α-ethyl-19-norprogesterone (FENP)
- ^{123}I-labeled *cis-11* β - methoxy-17α-iodovinylestradiol (Z-[^{123}I]MIVE)

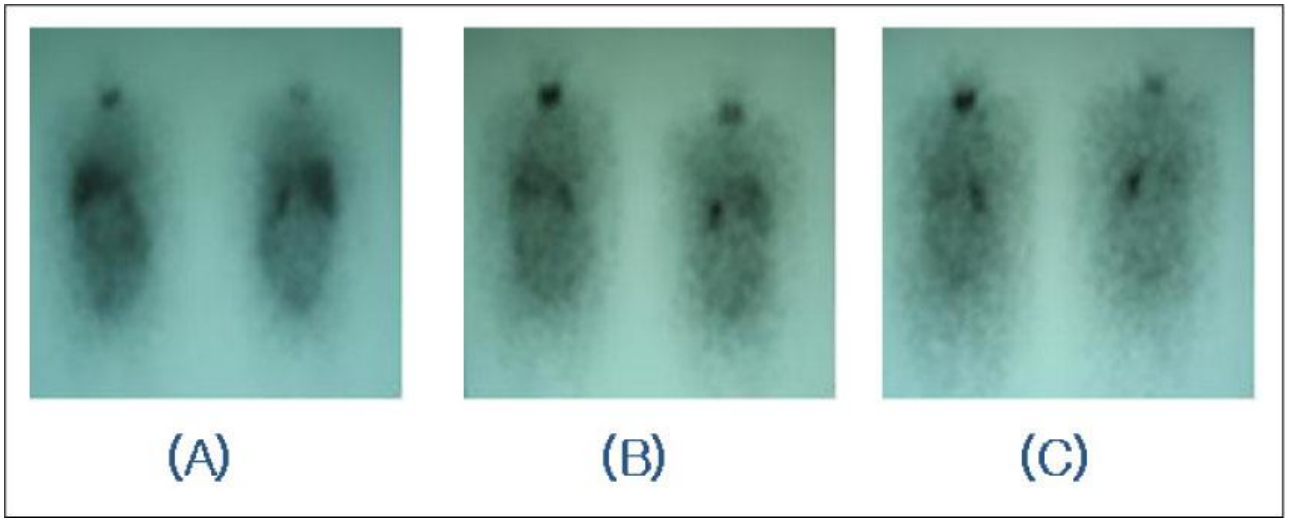
transported into the cell by passive diffusion and bind to steroid receptors within the nucleus

Specific Receptor Binding

LDL Receptors

Low-density lipoprotein (LDL) carries cholesterol to the adrenal glands as a substrate for synthesis of adrenal steroid hormones (cortisol and aldosterone)

- ^{131}I-6 β -iodomethyl-19-norcholesterol (NP-59) is the agent of choice for imaging patients with adrenal cortical diseases.
- Normal adrenal glands show bilateral symmetrical uptake of NP-59. Adrenal adenoma is identified as intense unilateral uptake while adrenal carcinoma shows no uptake of NP-59.



Whole body scans were obtained 3 days (A), 5 days (B), 7 days (C) after injection of I-131 NP59 1 mCi. Adrenal scan [59-[131I]iodocholesterol scanning (NP59 scan)] showed nodular activity in the region of left adrenal gland.

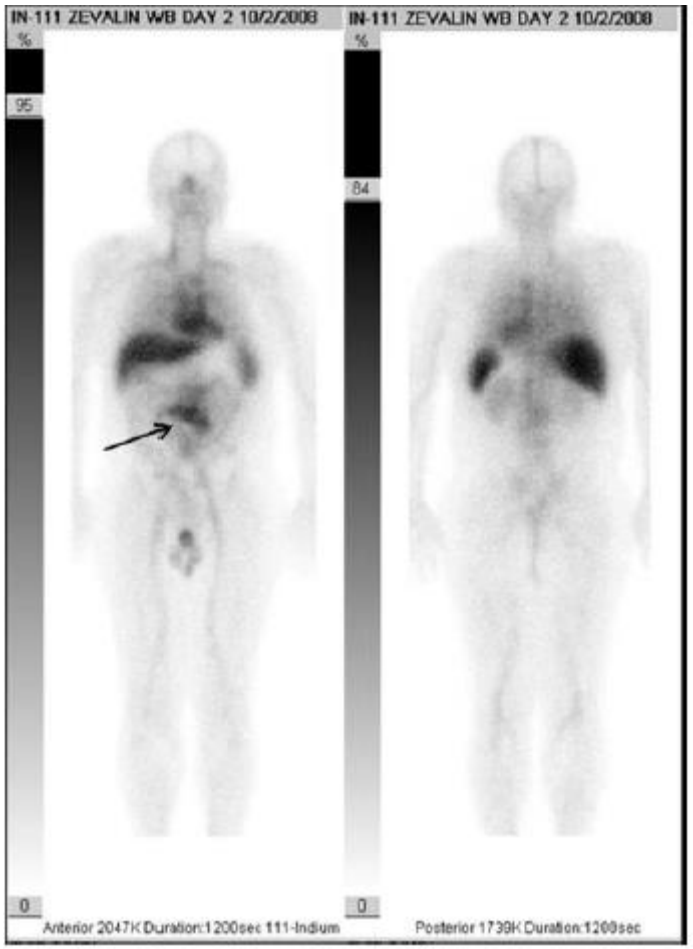
Kim et al., J Korean Soc Endocrinol. 2006 Feb;21(1):58-62

Specific Receptor Binding

Radiolabeled Antibodies

radioiodinated, ^{99m}Tc-labeled, ^{111}In- and ^{90}Y-labeled

I-131 tositumomab (Bexxar) and In-111/Y-90 ibritumomab tiuxetan (Zevalin), are monoclonal murine IgG antibodies directed to CD20 receptors on B-cells and non-Hodgkin's lymphoma tumor cells (treatment of NHL)



Pre-therapy In-111 ibritumomab tiuxetan image shows uptake in an abdominal lymphoma (arrow). Also seen is normal retention in blood pool, normal high uptake in liver and spleen, and normal low uptake in bone marrow and kidneys. This patient was subsequently treated with Y-90 ibritumomab tiuxetan.

Metabolism of drugs

Drug metabolism or biotransformation reactions are classified as:

Phase I functionalization reactions

Introduce or expose (unmask) a functional group (**-OH, -NH_2, -SH, -COOH) of the active substance**

- loss of pharmacological activity or
- formation of chemically reactive and more toxic, carcinogenic, or immunogenic metabolites

Phase II biosynthetic (conjugation) reactions

Formation of a covalent linkage between a functional group on the active substance or phase I metabolite with endogenously derived **glucuronic acid, sulfate, glutathione, amino acids, or acetate**

- Highly polar conjugates
- Generally are inactive and are excreted rapidly in the urine and feces

Metabolism of drugs

- The enzyme systems involved in Phase I reactions are located primarily in the *endoplasmic reticulum.*

These biotransforming reactions are carried out by:

Cytochrome P450 isoforms (CYPs) (mainly) and
Flavin-containing monooxygenase (FMO)
Esterases
Amidases, etc.

These reactions are catabolic (e.g. oxidation, reduction or hydrolysis).

- The phase II conjugation enzyme systems are mainly *cytosolic*

Cytochrome P450 (CYP)

- Cytochrome P450s (CYPs) are a superfamily of haem-thiolate containing enzymes which play a major role in the metabolism of many drugs and other xenobiotics.

  A number of carcinogens are also metabolised by CYPs and it is often these metabolites which are the ultimate carcinogenic species.

- CYPs catalyse the oxidation of bound substrates through the redox action of the hem moiety and the activation of molecular oxygen and are able to carry out a variety of hydroxylations, dealkylations and hetero atom oxidations.

Cytochrome P450 (CYP)

- Substrate specificity is very low for the CYP enzyme complex: *high lipid solubility is the only common property* that renders CYP substrates a wide variety of structurally unrelated drugs, ranging from a Mw of 28Da (ethylene) to 1203 Da (cyclosporine).
- Larger molecules (proteins) are not CYP substrates and little is known regarding their catabolism.

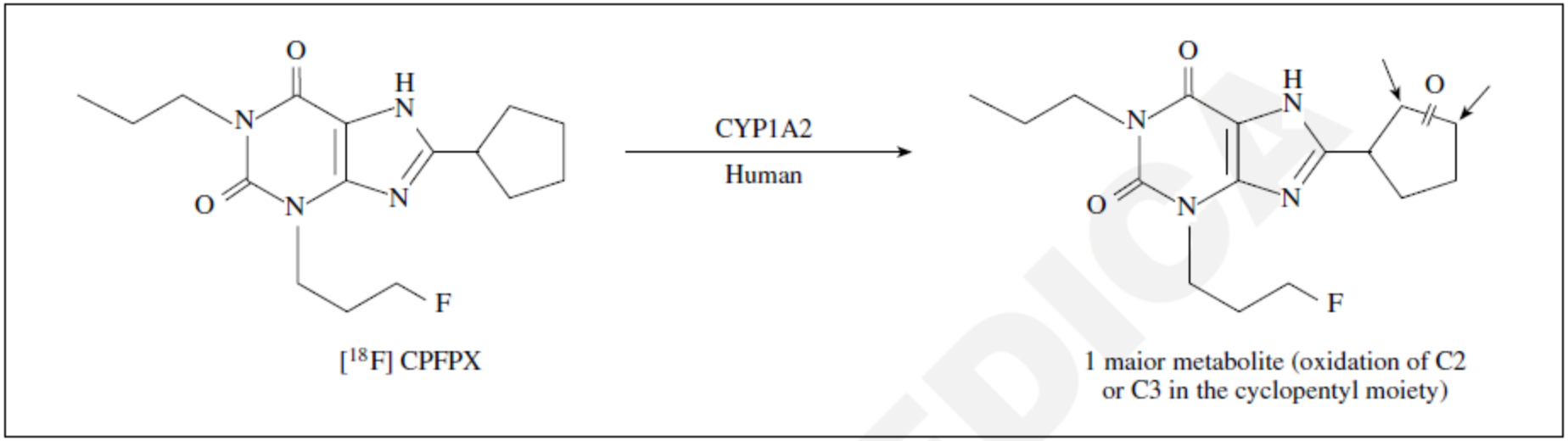
  It is believed that therapeutic proteins are metabolized by the same catabolic pathways as endogenous proteins, and can be broken down into amino acid fragments. Generally, the metabolic products of proteins are not considered a safety risk and classical biotransformation studies as performed for small molecules are not needed.

CYP-mediated metabolism of radiopharmaceuticals

[^{18}F]CPFPX

Implications of CYP-mediated metabolism during bolus/infusion PET studies in the pharmacokinetics of the radiotracer [^{18}F]CPFPX, a novel PET ligand used for *in vivo quantification of cerebral A1 adenosine receptors in glioma*.

In humans, this radioligand is metabolized to one major metabolite by CYP1A2 and at least 6 less abundant Phase I metabolites.



CYP1A2 –mediated preferential oxidation of [^{18}F]CPFPX

[^{18}F]CPFPX

- Its metabolism is expected to have a strict dependence on disease related or xenobiotic induced changes of CYP1A2 activity.

In patients with

- **liver disease (cirrhosis, hepatitis, etc.) or**
- exposure to CYP1A2 **inducers (tobacco smoke, carbamazepine, omeprazole, etc.)**
- **ihibitors (ciprofloxacin, phenacetine, etc.)**

it will result in an increase or decrease, respectively, in the metabolism of [^{18}F]CPFPX and thus alter its plasma clearance and quantization of cerebral A1 adenosine receptors

Metabolism of Radiometal-Labeled Proteins and Peptides

In the process of designing new radiometal-labeled mAbs and peptides for diagnostic imaging and targeted radiotherapy of cancer, the issue of metabolism of the radiopharmaceutical is often overlooked.

When evaluating a nuclear medicine image of a radiolabeled mAb or peptide (taken by either gamma scintigraphy or PET), a question arises as **what compound is actually being observed in the image?**

We can be **certain of the purity** of the radiopharmaceutical that was injected into the patient, but **most of the time we are not certain**

- **how rapidly the compound is metabolized**
- **the exact chemical form** of the radiolabeled metabolite that is present at the various imaging times post-injection.

Metabolism of Radiometal-Labeled Proteins and Peptides

The fate of the radionuclide, i.e., whether it remains bound to the mAb or peptide or whether it is metabolized, is of great significance, since this is what will ultimately determine the absorbed dose of the radiopharmaceutical to the tumor and normal tissues.

Understanding how radiometal-labeled proteins and peptides are metabolized requires taking several factors into consideration.

- the enzymatic breakdown of a protein or peptide into smaller peptide fragments that may or may not be attached to the radiometal chelate
- the enzymatic breakdown of the protein or peptide followed by acetylation or addition of another functional group
- dissociation of the radiometal from the chelator

Metabolism of Radiometal-Labeled Proteins and Peptides

The metabolism of radiometal-labeled mAbsis highly dependent on the radiometal.

e.g. The metabolism of ^{111}In-and ^{90}Y-labeled chelator-mAb/peptide conjugates has been shown to be significantly different than that of similar ^{64}/^{67}Cu-labeled protein and peptide conjugates.

One study* with animal models focused on the metabolism of the anti-colorectal carcinoma mAb ^{111}In-DTPA-1A3 and ^{111}In-DTPA-1A3-F(ab)2 in the liver and kidneys of rats. In the liver and kidneys **low MW metabolites were present, most likely ^{111}In-DTPA-Lys, but to a much greater extent in the kidneys than in the liver. Little or no evidence was observed for the dissociation of ^{111}In from DTPA in these tissues.**

*Rogers BE, FrananoFN, Duncan JR, Edwards WB, Anderson CJ, ConnettJM, Welch MJ. Identification of metabolites of In-111-DTPA-monoclonal antibodies and antibody fragments in vivo. *Cancer Res 1995;55: 5714s*.

Metabolism of Radiometal-Labeled Proteins and Peptides

The results of one study of DeNardo et al.* showed

a significant amount of lower MW metabolites (non-identified) of ^{111}In-and ^{90}Y-labeled 2IT-BAD-Lym-1

(2IT-BAD is 2-iminothiolane-2-[*p-(bromo-acetamido)benzyl]-1,4,7,10-tetraazacyclodo-decane-N,N9,N0,N-tetracetic acid)*

in the blood in non-Hodgkin's lymphoma patients and

normal volunteers (36% at 3 d post-injection);

they also determined that **there was no dissociation of these radiometals from the BAD chelator.**

*DeNardo GL, DeNardo SJ, Kukis DL, O'Donnell RT, Mirick GR, Meares CF. Metabolite production in patients with lymphoma after radiometal-labeled antibody administration. *J Nucl Med 2001;42:1324.*

Routes of drug elimination

- Urine (kidney)

- Secretion into the GI tract (feces)
- Liver
- Lung
- Other sites such as skin, milk, tears, saliva..

Mechanisms of renal excretion

- **Glomerular filtration**
  - Non-selective, unbound substances with molecular weight < 40,000 Da are eliminated by glomerular filtration.
  - Substances tightly bound to plasma proteins are not filtered by the glomeruli
- **Active tubular secretion**
  - many organic acids and some organic bases are actively secreted by renal tubules
- **Passive and active tubular reabsorption** lipid-soluble drugs tend to be reabsorbed by the renal tubules and are not excreted

Excretion and clearance of radiopharmaceuticals

Main pathways for excretion of RP:

Urine

Feces

Lungs (gases)

e.g. Radiolabeled peptides due to small Mw are excreted rapidly in urine.

- Effective clearance of radionuclide
- Effective levels on receptor (tumor) site???

Excretion and clearance of radiopharmaceuticals

The general formula for calculating clearance in first-order kinetics is:

$$CL = Vd \times ke$$

Vd = volumen of distribution
Ke= excretion constant

For RP, excretion is calculated easily by renal clearance of blood:

$$CL = U \times V \times 1/B$$

U = urinary concentration of the radiopharmaceutical
V = volume of urine per time
B = blood concentration of the radiopharmaceutical

Acknowledgement and further reading

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